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MEDICAL AND SOCIAL ASPECTS OF THE TREATMENT OF RHEUMATOID ARTHRITIS

WITH SPECIAL REFERENCE TO FACTORS AFFECTING PROGNOSIS

BY

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The hope that the problems of long-term treatment of rheumatoid arthritis had been solved by the discovery of the remarkable therapeutic effects of cortisone and ACTH has not been fulfilled. It would appear that in only a relatively small proportion of patients can symptoms be satisfactorily controlled over a long period without side-effects or complications (West and Newns, 1953). In the majority, reliance still has to be placed on the combination of local and general measures which experience has shown to be reasonably effective in maintaining function and preventing deformity. There is a serious danger at the present time that excessive interest in the therapeutic possibilities of new drugs or hormones may lead to a neglect of sound basic principles in the treatment of rheumatoid arthritis.

Few attempts have been made in the past to study the effect of a combination of medical and orthopaedic measures applied over a period of years. Accurate information on the value of such treatment is essential before the relative merits of new remedies can be assessed. Short and Bauer (1948) followed a group of 250 patients, treated on simple lines, for an average period of 9½ years; at the time of review 53·2 per cent. had improved, 12·8 per cent. had remained the same, and 34 per cent. had deteriorated; 15·2 per cent. of those who had improved were considered to be in complete remission. Ragan (1949) carried out a similar study on a group of 374 patients treated by a variety of methods, or not treated at all, and followed for an average period of 11 years. In his series, 48 per cent. had improved substantially, but in the other 52 per cent. the end result was poor. It would appear that, whatever form of treatment is applied, about 50 per cent. of patients suffering from rheumatoid arthritis will improve and 50 per cent. will do badly. It is against this background that the value of new methods must be judged. Although there is general agreement on the fundamental principles which should govern the treatment of rheumatoid arthritis, the application of these principles has been rendered difficult in the past by lack of hospital accommodation and adequate facilities. Doubts have been felt by many about the advisability of providing such accommodation in view of the heavy expense involved and the lack of clear proof that the course of the disease can be materially altered for the better.

The present study was designed to answer this question. Its immediate objects were:

(1) To reach an accurate assessment of the immediate results of treatment in hospital of patients with rheumatoid arthritis, as measured by changes in functional capacity and the activity of the disease process.

(2) To ascertain how long any improvement following hospital treatment could be maintained by adequate medical and social after-care.

(3) To estimate the extent of any changes in social and economic status following treatment and to determine the relationship of such changes to medical progress.

(4) To obtain information regarding factors which might be of significance in predicting the response to treatment of the individual patient.

Composition of the Group

The group for study consisted of all patients suffering from rheumatoid arthritis admitted to the Rheumatic Unit, Northern General Hospital, Edinburgh, between June, 1948, and July, 1951. All were considered to be in need of in-patient treatment, either because of active disease or the presence of deformities requiring correction. The original group totalled 307 patients. Fifteen patients had died since discharge, eight had left Scotland, and two failed to attend at follow-up, leaving 282 available for examination and assess-

ment. Basic information on these patients is given in Table I. Causes of death amongst the original group will be considered later.

TABLE I

BASIC INFORMATION ON 282 PATIENTS

Sex	Male	Female
Mean Age at Onset of Disease (yrs)	44·6	43·5
Mean Duration of Disease (yrs)	6·0	7·3
Mean Age on Admission (yrs)	50·6	50·5
Mean Duration of Hospital Treatment (wks) ..	10·0	8·9
Mean Period of Follow-up (mths)	24·4	24·4
Total No. of Patients ..	77 (27·3%)	205 (72·7%)

Age at Onset.—The mean age at the onset of the disease was 44·6 years in males and 43·5 years in females. The mean age at onset in a large series studied under the auspices of the Empire Rheumatism Council (E.R.C., 1950) was 42 years in males and 41 years in females.

Sex Incidence.—The ratio of females to males in this series was 2·7 : 1. This is comparable with that reported by other workers (E.R.C., 1950; Ragan, 1949).

Duration of Disease.—The mean duration of the disease up to the time of admission to hospital was 6 years in males and 7·3 years in females. It is of interest, however, to compare in more detail the duration of the disease before admission in males and females (Fig. 1). It will be seen that 30 per cent. of males were admitted within 6 months of the onset in contrast to 18 per cent. of females. Between 6 months and 5 years there is little difference between the sexes, but in cases of 5 years' duration and over on first admission, there is a greater proportion of females (females 44·4 per cent., males 32·5 per cent.).

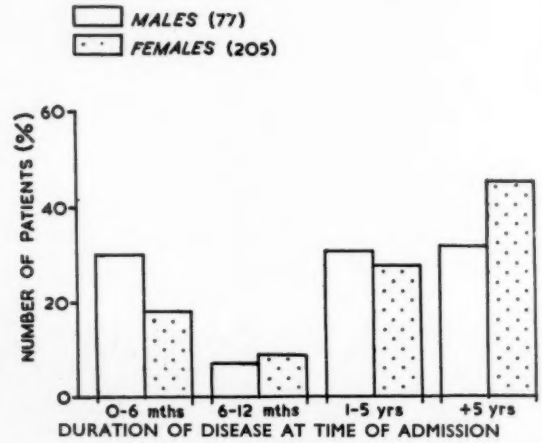

Fig. 1.—Duration of disease before admission to hospital, by sex.

Duration of Treatment in Hospital.—The average stay in hospital was 9 to 10 weeks, but the length of time ranged from 2 to 35 weeks. In the case of those patients severely crippled before admission, the processes of correcting deformities in weight-bearing joints and restoring muscular control and stability often took many weeks.

Duration of Follow-up.—The minimum period since discharge from hospital was 12 months; the maximum interval was 50 months, with a mean interval of 24·4 months. It is intended to continue this study, and the present communication only embodies the results of the first stage. Further review of these patients will be essential before any definite conclusions can be drawn regarding the ultimate value of hospital treatment followed by long-term medical and social care.

Previous Treatment.—67 patients (23·8 per cent.) had already received treatment as in-patients in other hospitals on account of rheumatoid arthritis, sixteen having been admitted on more than one occasion.

119 patients (42 per cent.) had been treated with gold on one or more occasions before admission; benefit had been temporary in the majority of cases.

35 patients (12·4 per cent. of the group of 282) required re-admission to the rheumatic unit after their initial period as in-patients. These re-admissions were necessitated by exacerbations of disease activity reported at the follow-up clinic.

Distribution of Affected Joints.—At the time of admission the disease was confined to the peripheral joints (hands, feet, wrists, and ankles) in nineteen cases; and to the central joints (shoulders, elbows, hips and knees) only in four cases. In the remaining 259 patients both peripheral and central joints were involved. Distribution was symmetrical in 46·8 per cent. of males and 52·3 per cent. of females.

Course of Disease.—The patients were divided into three groups in accordance with the type of course run by the disease up to the time of admission to hospital:

(1) A slowly progressive course without significant remissions.

(2) A course of exacerbations interspersed with apparent remissions in activity of the disease.

(3) A rapidly progressive course with marked systemic disturbance and without significant remissions.

There was no marked difference between males and females in this respect; 40 per cent. of males and 46 per cent. of females had run a course of exacerbation and remission; 22 per cent. of males and 14 per cent. of females had run a rapidly progressive course. In the remainder of both sexes the disease had been slowly progressive without significant remission.

When the type of course was considered in relation to the age at onset (Fig. 2), it was found that a rapidly progressive course was more common in the older age groups, particularly when the disease had started in persons over 60 years old, and that as the age at onset advanced, the frequency of the type characterized by exacerbations and remissions decreased.

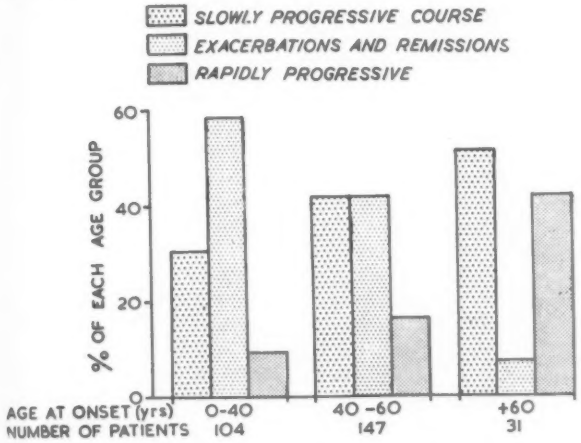

Fig. 2.—Relationship between type of course of disease and age at onset in 282 patients.

Deaths.—Between admission to hospital and the last follow-up examination, fifteen of the original 307 patients had died. The causes of death were as follows:

Malignant disease	4
Cardiovascular disease	5
Ulcerative colitis	2
Infective hepatitis	1
Fractured femur and pneumonia	1
Post-gastrectomy	2

The causes of death were not remarkable, although the occurrence of two deaths from ulcerative colitis in such a small series may be significant. None of the deaths could be related to the rheumatoid disease.

Co-existent Diseases.—The most common complicating conditions found affected the eyes or the skin. Signs of present or past disease of the eyes were present in 36 patients (12·8 per cent.). In another fourteen (5 per cent.) a diagnosis of psoriasis was made. Dermatitis was present in seven. As might be expected from the age distribution of patients in this group, signs of disease other than rheumatoid arthritis were relatively common, but in only fifteen cases was it considered that the complicating condition had materially interfered with the patient's progress. The nature of the disease in these patients was as follows:

Cardiovascular	9
Effects of old injury	2
Chronic nephritis	1
Carcinoma	1
Menorrhagia and anaemia	1
Perthe's disease	1

Psychological Factors.—In view of the widely-held opinion that psychological strain or emotional shock may be a factor in precipitating rheumatoid arthritis, special note was made of the incidence of such conditions. In only eleven patients (4 per cent.) in the present group was any history obtained of emotional stress immediately preceding the onset of arthritis. In 77 patients (27 per cent.) a history was obtained suggestive of psychological illness without a clear relationship to the onset of arthritis. This figure is not unduly high when compared with the incidence in the general hospital population. The Empire Rheumatism Council (1950) states that 25 per cent. of controls and 25 per cent. of cases of rheumatoid arthritis gave a history of some emotional disturbance within 2 years of onset.

From the data presented, it would appear that the group studied represents a reasonable cross-section of the rheumatoid population and that inferences drawn from the results of hospital treatment and after-care may provide a fairly reliable guide as to what can be expected from this regime.

Basic Regime in Hospital

The general principles of the basic regime employed have already been described in detail (Duthie, 1951). In the belief that all sufferers from rheumatoid arthritis will benefit from a period of rest, all patients spent a minimum of 2 weeks in bed after admission. During this period of rest, daily maintenance exercises were used to prevent unnecessary deterioration in the patient's general physical condition. Skin-tight plaster-of-paris splints were used to immobilize affected joints until the acute symptoms had subsided. Full doses of aspirin were prescribed. Local heat was applied to painful joints, but active exercises were deferred until signs of acute inflammation had begun to subside. The duration of this initial period of rest varied in individual patients, depending on the degree of activity of the disease. A fall in erythrocyte sedimentation rate, a gain in weight,

and an increased feeling of general well-being were regarded as indications that more active forms of treatment could safely be applied.

The second phase of treatment consisted of intensive efforts to restore joint stability by active and resisted exercises. No weight-bearing was allowed until this objective had been achieved in some measure at least.

The third phase aimed at restoring endurance and stamina by a progressive increase in weight-bearing, occupational therapy, and simple games.

Progress was graduated in accordance with age, disease activity, and the degree of residual damage in the affected joints. Gold was used in only 22 patients (7·8 per cent.) who failed to show a satisfactory response after a reasonable period on the basic regime. It should be borne in mind, however, that 42 per cent. of the patients in the group had already received one or more courses of gold before their present admission to hospital. Intravenous iron was used in 34 per cent. of cases on account of anaemia. It has been shown that, although the hypochromic, normocytic anaemia which is a constant feature of the active phases of rheumatoid arthritis is resistant to the administration of iron by mouth, a significant number of patients respond when iron is given by the intravenous route (Sinclair and Duthie, 1949, 1950; Ross, 1950; Jeffrey, 1952, 1953).

After-Care

Before discharge from hospital, patients were given detailed instruction in the use of simple home physiotherapy and remedial exercises. The importance of rest periods during the day and of wearing splints at night was emphasized. The role of the medical social worker in helping patients to regain social and economic stability will be discussed in detail later. Every patient was seen regularly at the follow-up clinic, and failures to report were investigated by letter or home visit. Fifty patients (17·7 per cent.) received further physiotherapy as outpatients. Splints were adjusted or new ones supplied when the need arose.

Methods of Assessment

Disease Activity.—This was assessed in the three grades shown in Table II; patients were grouped in these grades on admission to hospital, on discharge, and at the last follow-up examination.

Functional Capacity.—Four grades were used (Table III); patients were classified on admission, on discharge, and at follow-up. Functional capacity on admission was assessed on the basis of the patient's level of physical activity during the preceding 3 months.

TABLE III

GRADES OF FUNCTIONAL CAPACITY

Grade	Definition	Remarks
I	Fit for all normal activities	Full employment in usual work. Full house duties
II	Moderate restriction	Usual employment with modifications. Light or part-time work. All housework save the heaviest. No dependency on others
III	Marked restriction	Only very light work or light housework. Some degree of dependency on others
IV	Confined to chair or bed	Not capable of any work. Completely dependent on others

Clinical Progress.—At the final examination the clinical progress since admission to hospital was assessed under five headings:

Marked improvement
Moderate improvement
No change
Moderate deterioration
Marked deterioration

For the sake of uniformity, all the final medical examinations were conducted by a single observer (M.T.).

Social Factors.—Each patient was interviewed by the medical social worker (M.M.W.) on admission, on discharge, and at follow-up. The following factors were considered:

Social category (Registrar-General)
Employment
Income level
Housing conditions
Domestic needs
Family background

All adjustments of adverse social or economic circumstances during the stay in hospital and after discharge were noted. At the final review the improvement or deterioration of the patient's social circumstances was assessed.

TABLE II

GRADES OF DISEASE ACTIVITY

Grade	Degree of Activity	Blood Sedimentation Rate (mm./hr)	Haemoglobin (per cent.)	Joint Involvement	Systemic Disturbance
1	Very active	Over 60	65 or under	Signs of acute inflammation in many joints	Marked, with loss of weight
2	Moderately active	20–60	65–85	Signs of activity in several joints	Moderate, weight steady
3	Inactive	20 or under	85 or over	No symptoms due to inflammation in the joints	None

Results

Functional Capacity.—The distribution of patients over the four grades on admission, on discharge, and at follow-up is shown in Fig. 3. On admission 62 (22·0 per cent.) were confined to bed and 120 (42·6 per cent.) markedly incapacitated; these two grades accounted for 64·6 per cent. of the whole group. On discharge the proportion in Grades III and IV fell to 24·5 per cent. and only one patient was still bedridden, but at follow-up an additional six patients had relapsed to the bedridden level. On admission no patients were placed in Grade I, but at the time of discharge 32 (11·3 per cent.) were so graded; at follow-up the number in Grade I had increased to eighty (28·4 per cent.), and 72·4 per cent. of patients were placed in Grades I or II. More detailed analysis of the data on discharge showed that 136 patients had improved sufficiently to justify their advance by one grade and that 34 had advanced by two or more grades. At the final review one hundred cases had advanced by one grade and seventy had moved up two or more grades. The fall by 36 of those improving by one grade and the increase by 36 in those improving by two or more grades indicates that substantial further improvement in functional capacity had taken place in 36 patients between discharge and follow-up. When the degree of improvement between discharge and follow-up was tested for statistical significance, the increase in functional capacity was shown to be highly significant ($\chi^2 = 31{\cdot}8$ with 2 d.f. $P < 0{\cdot}001$).

The number of patients who had improved sufficiently in functional capacity to justify moving them up one or more grades at the last follow-up examination totalled 170 (60·3 per cent.).

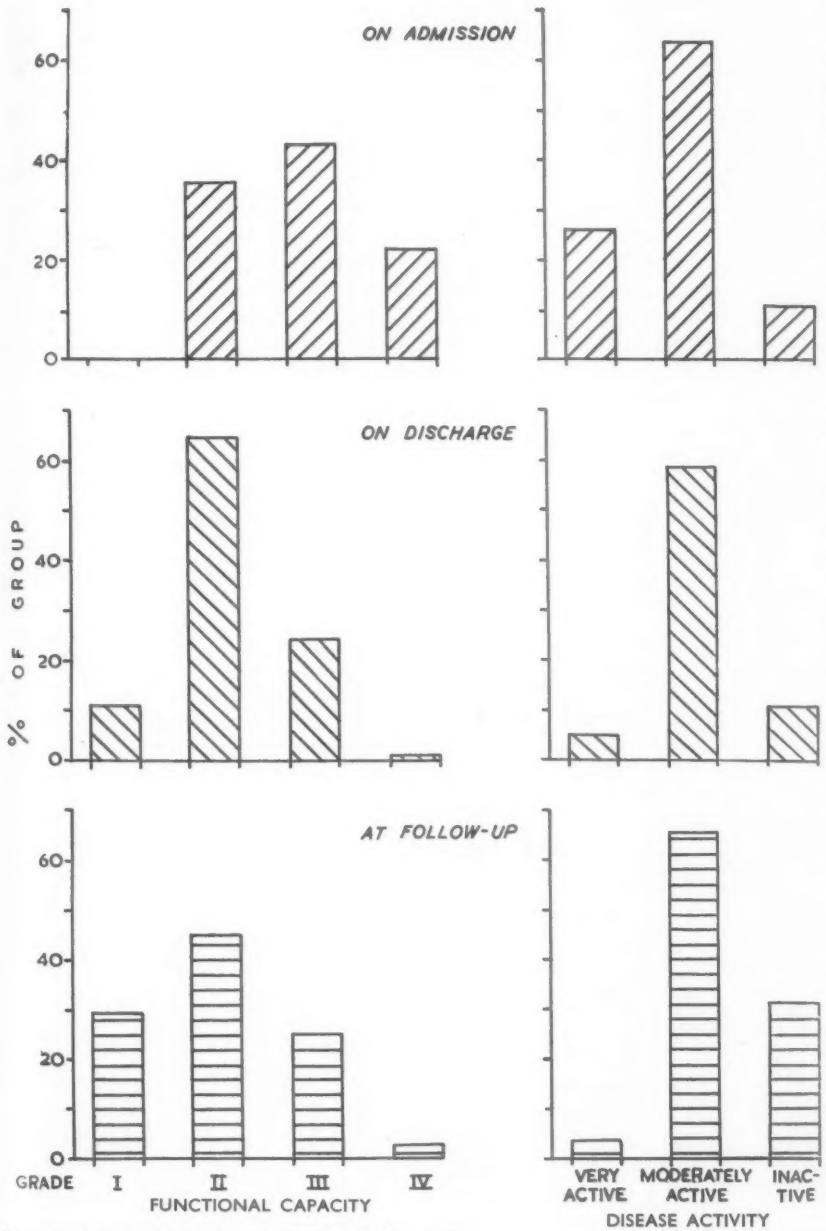

Fig. 3.—Grades of functional capacity before and after hospitalization.

Fig. 4.—Grades of disease activity before and after hospitalization.

Disease Activity.—The changes in disease activity between admission, discharge, and final follow-up are shown in Fig. 4. Between admission and discharge there was a marked decrease. Those graded "very active" dropped from 26·2 to 5·0 per cent., and the proportion classed as "inactive" rose from 10·3 to 35·8 per cent. There was no significant increase in disease activity between discharge and follow-up.

The relationship between disease activity and functional capacity was subjected to statistical analysis. On admission there was a close correlation between them. A χ^2 test showed a value for χ^2 of 18·2; $P < 0{\cdot}001$. As would be expected, the number of very active cases was significantly greater in the group with the most severe functional incapacity.

On discharge the correlation was not significant ($\chi^2 = 2{\cdot}6$; $0{\cdot}4 > P > 0{\cdot}3$). The decrease in disease activity was more marked than the gain in functional capacity. Both had improved, but not equally.

At follow-up, however, the close relationship between the two had been re-established ($\chi^2 = 19{\cdot}64$ $P < 0{\cdot}001$).

These figures indicate that the activity of the disease process, as judged by the standards adopted, can be substantially reduced by treatment in hospital. This reduction can apparently be maintained in the majority of patients for a reasonable length of time after discharge. Functional capacity continues to improve in a significant number of patients in the months following discharge, although the disease activity remains at about the same level.

Clinical Progress.—The results of the general assessment of clinical progress are shown in Fig. 5. This type of assessment is largely influenced by the impressions of the examining physician and the opinions expressed by patients at follow-up. 70·5 per cent. of patients were graded as moderately or markedly improved (males 76·7 per cent., females 68·3 per cent.), but it will be recalled that only 60·3 per cent. had improved sufficiently to justify moving them up one or more grades in functional capacity. The difference between these figures may be accounted for by the fact that there is considerable room for improvement in both symptoms and physical signs within each grade of functional capacity, but in about 10 per cent. of cases this was insufficient to justify up-grading. The assessment of progress in terms of functional capacity represents a more objective measure of improvement and is to be preferred in any realistic attempt to evaluate the results of treatment.

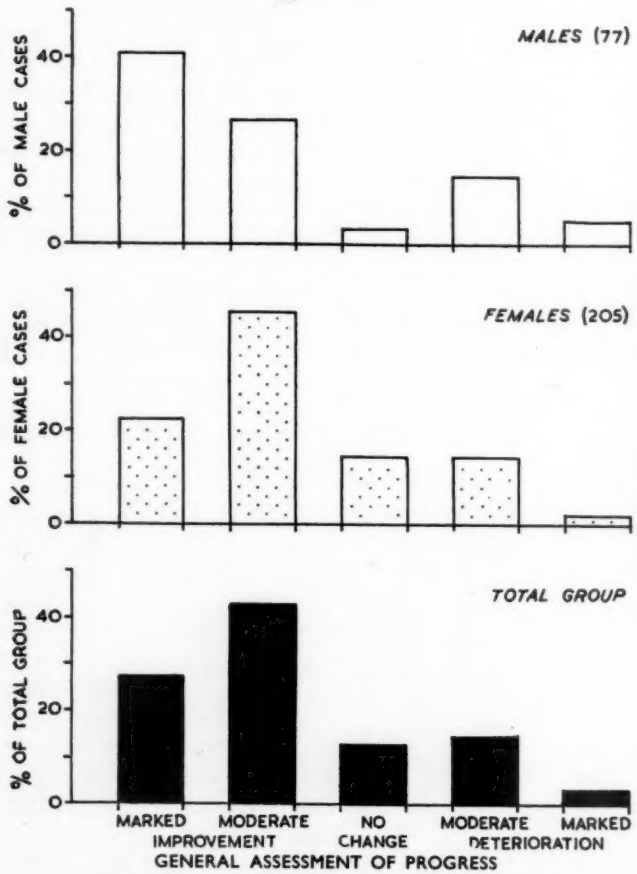

Fig. 5.—General assessment of clinical progress, by sex.

Capacity for Work.—Although a diminution in the activity of the disease process and improvement in functional capacity are valuable in themselves and may do much to restore personal independence, the process of rehabilitation must include the restoration to economic independence in cases where this is a practical possibility. Of 282 patients, 171 were housewives, eleven had retired, 23 had given up work because of marked degrees of incapacity, one was a schoolchild, and 76 had been in gainful employment within the year preceding admission. Only in these 76 cases was it possible to assess the direct effect of treatment in hospital on capacity for work. These patients were classified in four groups in accordance with their capacity for work on admission and at follow-up (Table IV, opposite):

(1) Fit for normal employment.
(2) Fit for light work.
(3) Unfit for work.
(4) Fit but unemployed.

Only four of the 76 patients were considered fit for normal employment on admission. At follow-up, 29 were employed full-time under normal conditions, 33 were employed in light work, and only fourteen remained without employment. Of these, five

TABLE IV

CAPACITY FOR WORK IN 76 CASES

Capacity for Work	On Admission		At Follow-up	
	No.	%	No.	%
(1) Normal Employment	4	5·3	29	38·2
(2) Light Work	14	18·4	33	43·4
(3) Nil	58	76·3	9	11·8
(4) Fit but Unemployed	0	—	5	6·6
TOTAL	76	100	76	100

were considered fit for some form of work, but had been unable to find a suitable job.

The 171 housewives' capacity for work in the home was assessed in four categories on admission, on discharge from hospital, and at follow-up (Table V):

(1) Fit for all housework.
(2) Fit for all but the heaviest tasks (e.g. scrubbing floors, heavy washing, etc.).
(3) Fit only for light duties.
(4) Unfit for housework in any form.

TABLE V

HOUSEWIVES' CAPACITY FOR HOUSEWORK

Fitness for Work	On Admission		On Discharge		At Follow-up	
	No.	%	No.	%	No.	%
(1) All work	0	—	5	2·9	27	15·8
(2) All duties save the heaviest	15	8·8	71	41·5	78	45·6
(3) Light housework only	87	50·9	83	48·6	47	27·5
(4) Nil	69	40·3	12	7·0	19	11·1
TOTAL	171	100	171	100	171	100

On admission 40·3 per cent. had been placed in Category 4, and the proportion in this grade had diminished to 11·1 per cent. at follow-up. The proportion fit for all but the heaviest duties rose from 8·8 on admission to 45·6 per cent. at follow-up; 61·4 per cent. were in Categories 1 and 2 at follow-up, 15·8 per cent. being fit for all household duties.

It would then appear that there is good correlation between the medical assessment of functional capacity and actual fitness for work in those groups of patients where this can be checked with reasonable accuracy.

Social and Economic Factors

Rheumatoid arthritis is an incurable condition. Although medical treatment can reduce the activity of the disease and improve functional capacity, only a relatively small proportion of patients become free from symptoms and are left without residual disability. The majority have to accept some restriction of their activities and adjust their lives accordingly. The process of adaptation to a reduction in physical capacity forms an integral part of the rehabilitation of these patients. It is in this connection that social and economic factors assume great importance. These were investigated in detail by the medical social worker in every case. A wide variety of factors can exercise an adverse effect on rehabilitation and only an analysis on broad lines is possible. Difficulties may arise in connection with continued medical care, domestic arrangements, employment, personal relationships, finance, and housing. The incidence of such factors in the group is shown in Table VI. Only eighteen patients required no assistance from the medical social worker. In the remaining 264, help was given on 651 occasions, an average of 2·46 items of service for each patient.

TABLE VI

ADVERSE SOCIAL CIRCUMSTANCES IN 282 PATIENTS

No.	Definition	No.	%
I	Nursing and Medical	165	24·8
II	Domestic	106	15·9
III	Employment	80	12·0
IV	Personal	69	10·3
V	Marital and Family	62	9·3
VI	Financial	50	7·5
VII	Environmental	35	5·2
VIII	Miscellaneous	100	15·0
TOTAL		667	100·0

At the final review an improvement in social circumstances was seen in 74·1 per cent.; in 19·1 per cent. there was no change; in 6·8 per cent. (nineteen patients) there had been some deterioration. The influences leading to this deterioration in these nineteen patients fell under the following heads:

Medical	12
Psychological	5
Environmental	1
Industrial	1

There was a close correlation between medical and social improvement. Only four patients whose arthritis showed moderate or marked improvement were found to have deteriorated in social circumstances, the causes being death of husband, unemployment, development of pulmonary tuberculosis, and low intelligence respectively.

There was no significant difference between the sexes with regard to improvement in social circumstances (males 77·9 per cent.; females 72·7 per cent.).

The duration of the disease before admission to hospital was an important factor, as is shown by the percentage improvement in the four groups: under 1 year 88 per cent.; 1 to 5 years 72·8 per cent.; 5 to 10 years 71·4 per cent.; over 10 years 59·7 per cent.

There was no striking correlation between social improvement and economic class in the majority of instances, but the group of unskilled labourers fared worst (58 per cent. improved , as against 75-84 per cent. in other classes).

Housing conditions did not appear to exercise a significant influence on progress after hospital treatment. The changes in functional capacity and the overall estimate of progress at follow-up were not appreciably different in 56 patients found to be living in unsatisfactory houses from those in the group as a whole.

In respect of 171 housewives, the capacity for housework at follow-up was considered in relation to changes in social circumstances as assessed by the medical social worker. It was found that of 27 patients classified as fit for all household duties, 25 (92·6 per cent.) showed improvement in social circumstances. Among 78 fit for modified duties (*i.e.* all but the heaviest tasks) seventy (87·7 per cent.) improved socially. Amongst those classed as fit for light duties only, or as totally unfit for all housework (66 patients) only thirty (45·4 per cent.) showed any improvement in social circumstances at follow-up. It is clear that for the great majority of women engaged in household duties improvement in the medical sense leads to a corresponding improvement in living conditions in relation to the family group, provided skilled advice and assistance are available after discharge from hospital.

Earning Capacity.—The assessment of the effect of the disease on earning capacity was very difficult in this mixed group of patients, many of whom were housewives. However, the medical social worker made as accurate an assessment as possible of the changes in the family income in all 282 cases. An average for the 6 months preceding admission was compared with the level at the time of follow-up. In fifty patients the family income had improved because the patient's earnings had increased after discharge from hospital. In 41 cases income had improved as a result of increased pensions and allowances to the patient, or because of the increased earnings of other members of the family. In 186 cases there had been no significant alteration in the family income. In five instances there had been a fall in income, but only in three could this be directly attributed to decreased earning capacity on the part of the patient. An analysis of results of treatment in the fifty patients whose earnings had increased showed that 86 per cent. had improved medically as compared with 70·5 per cent. of the group as a whole.

Type of Employment.—In many cases employment problems can be solved only if skilled advice and guidance are available on discharge from hospital. The medical social worker plays an important part at this stage, though her advice is not always followed. To assess the value of her work in this sphere, a comparison was made between the social circumstances at follow-up of three groups:

(*a*) nineteen patients whose previous employment was regarded as suitable;
(*b*) 41 patients who found suitable employment as a direct result of action taken by the medical social worker;
(*c*) 31 patients who sought and found employment on their own account.

In Groups (*a*) and (*b*) combined, 83·2 per cent. were rated as having improved in social circumstances, whereas, in Group (*c*) only 67·7 per cent. showed improvement. These figures suggest that work regarded as suitable from the medical point of view more frequently leads to improvement in social circumstances than work found by the patients on their own account. The factors influencing the patients' response to advice regarding employment are many and complex, but where such advice and help can be accepted, results in terms of satisfactory resettlement would appear to justify the action taken.

Prognosis

The main difficulty in assessing the value of any form of treatment of rheumatoid arthritis lies in the fact that it is rarely possible to forecast the future course of the disease in an individual patient. Short and Bauer (1948) stated that in their group males appeared to fare a little better than females: the subsequent course was milder if the disease began below the age of 40, and if the joint involvement at the onset was asymmetrical; those below normal weight on admission to hospital did badly. The most striking factor affecting prognosis was found to be the duration of the disease before treatment was instituted. Patients treated within 1 year of the onset of symptoms showed a much more marked degree of improvement than those in whom the disease was of longer duration. Observing 250 cases of rheumatoid arthritis for an average period of 6 years, Bywaters and Dresner (1952) found that

certain factors were associated with a favourable prognosis: males on the whole did better than females; low age at onset, short duration of illness, a low E.S.R., absence of anaemia, and absence of radiological changes in the joints at first attendance were all of favourable significance.

A detailed study of all the possible factors which might influence the prognosis was not considered justified in the present group, in view of the relatively short duration of follow-up, but attention was given to a few of the more obvious.

Duration of Disease.—From the information available it appeared likely that the duration of the disease before admission to hospital might be the most important factor in determining the response to treatment. For this reason it was decided to study this aspect first in the hope that an accurate estimate of its importance might make it easier to assess the relative significance of other possible influences on prognosis.

The relationship between the duration of the disease and the functional capacity on admission was examined first. It was found that the patients were evenly distributed among the four grades, irrespective of duration of disease. It was obvious, therefore, that duration of disease had no influence on functional capacity as assessed on admission. A similar analysis of the results on discharge from hospital (Table VII) revealed that 85·7 per cent. of those admitted during the first year of the disease and 83·9 per cent. of those admitted between the first and fifth year were placed in Grades I or II. In patients with disease of longer duration the results were much poorer: only 59·2 per cent. of patients in the 5 to 10-year group, and 64·7 per cent. in the over 10-year group reached the two upper grades.

TABLE VII

RELATIONSHIP BETWEEN FUNCTIONAL CAPACITY ON DISCHARGE AND DURATION OF DISEASE

Duration of Disease on Admission (yrs)	Functional Capacity on Discharge					
	Grades I and II		Grades III and IV		TOTAL	
	No.	%	No.	%	No.	%
Under 1 ..	72	85·7	12	14·3	84	100
1—5	68	83·9	13	16·1	81	100
5—10	29	59·2	20	40·8	49	100
Over 10 ..	44	64·7	24	35·3	68	100
TOTAL ..	213	75·5	69	24·5	282	100

At follow-up (Table VIII) the corresponding figures were 83·3, 75·3, 65·3, and 60·3 per cent. Functional capacity had been well maintained in the majority of patients, but the differences between patients with disease of under or over 5 years' duration remained statistically significant.

TABLE VIII

RELATIONSHIP BETWEEN FUNCTIONAL CAPACITY AT FOLLOW-UP AND DURATION OF DISEASE

Duration of Disease on Admission (yrs)	Functional Capacity at Follow-up					
	Grades I and II		Grades III and IV		TOTAL	
	No.	%	No.	%	No.	%
Under 1 ..	70	83·3	14	16·7	84	100
1—5	61	75·3	20	24·7	81	100
5—10 ..	32	65·3	17	34·7	49	100
Over 10 ..	41	60·3	27	39·7	68	100
TOTAL ..	204	72·4	78	27·6	282	100

The duration of disease was considered in relation to the number of grades of function gained or lost as assessed at follow-up. 78·6 per cent. of those admitted in the first year of the disease and 65·4 per cent. of the 1 to 5-year group had moved up one or more grades, as compared with 46·9 per cent. in the 5 to 10-year group, and 41·2 per cent. in the over 10-year group. The differences between the results in the under 5-year group and in the over 5-year group are statistically significant. Cases admitted during the first year consistently show the most marked and sustained improvement.

When duration of disease at the time of admission was considered in relation to the physician's general assessment of progress at follow-up, a similar pattern emerged. 84·5 per cent. of early cases showed moderate or marked improvement; 69·1 per cent. of the 1 to 5-year group; 67·3 per cent. of the 5 to 10-year group, and only 57·3 per cent. of the over 10-year group improved to the same extent. The greater measure of improvement seen in the cases of shorter duration is statistically significant.

The number of cases considered to be inactive on admission, on discharge, and at follow-up were studied (Table IX). The number classed as inactive amongst early cases (under 1 year) rose from five (6 per cent.) on admission to 24 (28·5 per cent.) on

TABLE IX

INACTIVE CASES ON ADMISSION, ON DISCHARGE, AND AT FOLLOW-UP IN RELATION TO DURATION OF DISEASE ON ADMISSION

Duration of Disease on Admission (yrs)	No. of Cases	Inactive Cases (per cent.)		
		On Admission	On Discharge	At Follow-up
Under 1 ..	84	6·0	28·5	40·5
1—5	81	12·3	39·5	30·9
5—10 ..	49	12·3	38·8	18·4
Over 10 ..	68	11·8	38·3	28·0
TOTAL ..	282	10·6	36·3	29·4

discharge, and to 34 (40·5 per cent.) at follow-up. Although the number of inactive cases had increased on discharge amongst patients with disease of longer duration, the increase was not maintained at follow-up.

These results confirm the findings of Short and Bauer (1948). They must be borne in mind when considering the influence of other factors which may affect the response to treatment in hospital. The possibility must also be considered that factors other than duration of disease may influence response in patients admitted early in the disease.

Age at Onset.—This was considered in relation to the functional capacity at follow-up and the results are shown in Table X. The figures show no statistically significant differences in the effect of the disease on functional capacity in the various age groups.

TABLE X
RELATIONSHIP BETWEEN FUNCTIONAL CAPACITY AT FOLLOW-UP AND AGE AT ONSET OF DISEASE

Age at Onset (yrs)	Number of Patients	Graded I and II at Follow-up	
		No.	%
Under 40 ..	104	77	74·0
40—60	147	106	72·1
Over 60	31	21	67·7

To ascertain whether the age at onset bore any relationship to the capacity of patients to benefit from treatment, the degree of improvement in functional capacity in the three age groups was compared (Table XI). From these figures it appears that patients who contract the disease late in life respond remarkably well to treatment. It should be noted, however, that more patients in the oldest age group were admitted to hospital within 1 year of onset of the disease (74 per cent.), than in the 40 to 60-year group (30 per cent.), and the under 40-year group (17·4 per cent.).

TABLE XI
PERCENTAGE IMPROVEMENT IN FUNCTIONAL CAPACITY AT FOLLOW-UP RELATED TO AGE AT ONSET OF DISEASE

Age at Onset (yrs)	Number of Patients	Improvement in Functional Capacity	
		By 2 or more grades	By 1, 2, or more grades
Under 40	104	23·0	51·9
40—60 ..	147	24·5	61·9
Over 60 ..	31	32·2	77·4

It appeared possible that the favourable influence of early admission to hospital might be responsible for the good response to treatment in the older age group. This was investigated by considering the duration of the disease on admission in patients grouped according to age at onset. It was found that no significant difference could be demonstrated which was due to age at onset alone. The factor of age at onset did not therefore appear to be of any prognostic significance in respect of the immediate response to treatment. This does not imply that the long-term prognosis is necessarily the same at all ages.

Sex.—Table XII shows the distribution of males and females in the four grades of functional capacity on admission, on discharge, and at follow-up. There was no marked difference between the sexes on admission and on discharge. There was, however, a striking change in pattern at the time of follow-up, when 41·5 per cent. of males had reached Grade I as compared with only 23·4 per cent. of females, and 32·2 per cent. of females remained in Grades III and IV, as compared with only 15·6 per cent. of males.

TABLE XII
COMPARISON OF RESULTS OF TREATMENT IN 77 MALES AND 205 FEMALES, AS MEASURED BY PERCENTAGE CHANGES IN FUNCTIONAL CAPACITY

Grade of Functional Capacity	On Admission		On Discharge		At Follow-up	
	Males	Females	Males	Females	Males	Females
I ..	—	—	7·8	12·7	41·5	23·4
II ..	36·4	35·1	75·3	60·0	42·9	44·4
III and IV	63·6	64·9	16·9	27·3	15·6	32·2

The results of assessment of disease activity on admission, on discharge, and at follow-up (Table XIII) show a similar trend; at follow-up 42·9 per cent. of males and only 26·3 per cent. of females were graded as inactive.

TABLE XIII
COMPARISON OF PERCENTAGE CHANGES IN DISEASE ACTIVITY IN 77 MALES AND 205 FEMALES

Degree of Disease Activity	On Admission		On Discharge		At Follow-up	
	Males	Females	Males	Females	Males	Females
Inactive ..	10·4	10·2	44·2	32·7	42·9	26·3
Moderate	71·4	60·5	53·2	61·5	55·8	69·3
Marked ..	18·2	29·3	2·6	5·8	1·3	4·4

All these differences between the sexes in respect of functional capacity and disease activity are statistically significant.

Investigation of the factor of early admission to hospital revealed that 36·5 per cent. of the males were admitted during the first year of the disease, in comparison with 27·7 per cent. of the females. When the influence of early admission upon the response to treatment in the two sexes was investi-

gated, no significant difference was found; 89·3 per cent. of males admitted to hospital within the first year reached Grades I and II, compared with 80·4 per cent. of females. In cases of longer duration, the females did not improve as markedly as the males, but the difference was not statistically significant in any of the modes of improvement measured.

It would thus appear that males generally fare better than females, except in cases admitted to hospital within the first year, when the response to treatment is equally good in both sexes.

Activity of Disease on Admission.—Patients were classed as inactive, moderately active, or markedly active on admission to hospital. Only 29 were inactive, and comparison was made at follow-up between the progress of those considered to be moderately active on admission with that of those showing signs of marked activity. Of the moderately active group (179 patients), 69·7 per cent. were assessed as showing moderate or marked improvement. Of the markedly active group (74 patients), 71·6 per cent. showed moderate or marked improvement. Thus the degree of disease activity as assessed on admission to hospital did not appear to exercise any marked influence on the subsequent progress of the patients in this series.

The two main groups of marked and moderate disease activity were further examined, to ascertain whether the factor of early admission to hospital had unduly influenced the prognosis in either. It was found that early cases did equally well, irrespective of whether they were moderately active (78·8 per cent. improved) or markedly active (74·1 per cent. improved) on admission. The small group of cases characterized by long duration and marked disease activity did extremely badly when judged by ultimate functional level, grades of functional capacity improved, or physicians' assessment of progress. Disease activity is thus of no value as a factor in the assessment of prognosis, except when a severe degree of activity is associated with long duration of disease.

Type of Course of Disease.—The course run by an individual patient suffering from rheumatoid arthritis may vary over the years and only a very broad classification is possible. As previously noted, the patients were divided into three groups:

(1) Slowly progressive.
(2) Exacerbations and remissions.
(3) Rapidly progressive.

The results of treatment in terms of functional capacity, as assessed at follow-up, were compared in the three groups (Table XIV). The number of patients in Group 3 is relatively small (46) in comparison with the other two groups (111 and 125), but there is an impressive difference in the results of treatment.

TABLE XIV

RELATIONSHIP BETWEEN TYPE OF COURSE AND CHANGES IN FUNCTIONAL CAPACITY

Grade of Functional Capacity at Follow-up	Type of Course of Disease					
	Slowly Progressive		Remissions and Exacerbations		Rapidly Progressive	
	No.	%	No.	%	No.	%
I	26	23·4	29	23·2	25	54·3
II	49	44·2	58	46·4	17	37·0
III	32	28·8	35	28·0	4	8·7
IV	4	3·6	3	2·4	0	—
TOTAL	111	100	125	100	46	100

When the 84 cases admitted within 1 year of onset were classified by type of course, 38 were placed in Groups 1 and 2 and 46 in Group 3. On admission, fourteen (30·4 per cent.) of the rapidly progressive cases (Group 3) and thirteen (34·2 per cent.) of the rest (Groups 1 and 2) were placed in Grade II functional capacity. This difference is not significant. On discharge, 42 (91·3 per cent.) rapidly progressive cases and thirty (79 per cent.) of the other two types were placed in functional Grades I and II. The difference does not reach the level of statistical significance, although it is in favour of the rapidly progressive cases. At follow-up, 41 (91·3 per cent.) of the rapidly progressive types were in Grades I and II, compared with 28 (73·7 per cent.) of the other two types. Although the difference again fails to reach the level of statistical significance ($\chi^2 = 3{\cdot}46$ with 1 d.f. $0{\cdot}1 > P > 0{\cdot}05$) it is worth noting that there is a consistent difference which favours cases with a rapidly progressive course.

The overall assessment of progress was used to estimate improvement in patients grouped according to the type of course and the duration of the disease. Of the 46 patients running a rapidly progressive course (Group 3), all of whom were admitted within 1 year of the onset, 87 per cent. had improved markedly or moderately in comparison with 81·6 per cent. of the other two groups of patients (Groups 1 and 2) admitted within 1 year of onset. The difference is not significant. Of the patients admitted between 1 and 5 years of onset (all belonging to Groups 1 and 2), only 69·1 per cent. showed moderate or marked improvement.

When improvement by grades of functional capacity was used as the measure of progress, 82·6 per cent. of the rapidly progressive group were found to have advanced by one or more grades, in comparison with 71 per cent. of the other groups admitted within the first year. The 1 to 5-year group showed an improvement in 65·4 per cent. cases. The difference between the rapidly progressive cases and the others admitted within 1 year is again not statistically significant, but it probably constitutes a real difference.

Distribution of Affected Joints.—In view of the statement of Short and Bauer (1948) that the prognosis was worse in those patients in whom the joints were symmetrically affected at the onset of the disease, patients were grouped by symmetry or asymmetry of joint involvement on admission, to assess the response to treatment in the two groups. In 143 patients involvement was symmetrical. In 139 it was asymmetrical. There was no significant difference between the two groups in regard to functional capacity on admission, and as judged by improvement in functional capacity at follow-up, the progress of the two groups was very similar. It was therefore considered that the pattern of joint involvement at the time of admission was of no value in predicting the response to treatment.

Economic Class on Admission.—It was possible to divide 117 patients into two groups, those in the professional and clerical classes (38 patients) and those in the manual skilled, semi-skilled, and unskilled classes (79 patients). Functional capacity in the two groups at follow-up were compared. It appeared that professional and clerical workers did less well on the whole than manual workers; only 26·3 per cent. of the former became fit for all normal activities as opposed to 41·7 per cent. of the latter. This was confirmed by the assessment of change in functional capacity at follow-up; 52·6 per cent. of the professional or clerical workers were moved up one or two grades as compared with 69·6 per cent. of the manual workers. Although the better response of the manual workers does not attain the level of statistical significance, it is a noteworthy and rather surprising finding.

Type of Work.—In view of the possibility that those engaged in manual work derived greater benefit from hospital treatment than those in more sheltered occupations, a further examination of the nature of employment in relationship to results of treatment was made in 115 patients. Work was classified as heavy, medium, or light, on the basis of the degree of physical effort required in its performance. Employment was classed as heavy in twenty patients, medium in 51, and light in 44. In order to simplify comparison, the results in the groups performing heavy and medium work were combined and compared with those in patients doing light work. In the assessment of functional capacity at follow-up, 67·6 per cent. of the medium and heavy workers were moved up one or more grades as compared with 56·8 per cent. of those in light work. Although the difference does not reach the level of statistical significance, the more favourable response of the medium and heavy workers is a finding of some interest. It indicates at least that manual labour does not exert an unfavourable effect upon the response to treatment, and it may be that rehabilitation is easier in people accustomed to relatively strenuous effort in the course of their daily activities.

Degree of Disability on Admission.—To assess the effect on prognosis of the degree of disability on admission to hospital, patients were grouped in accordance with their initial functional grading. On admission no patients were placed in Grade I. The changes in the other three grades at discharge and follow-up were compared. Those with moderate impairment of function on admission showed the greatest degree of improvement, 99 per cent. being found in Grades I and II on discharge, and 88 per cent. still in those grades at follow-up, the total in Grade I having increased by ten. The groups with marked impairment of function or confined to bed or chair showed a much less striking degree of improvement when assessed on discharge and at follow-up. These figures emphasize the need for early treatment in hospital if the best results are to be obtained.

Haemoglobin Level on Admission.—Anaemia of greater or lesser degree is a common feature of the active phase of rheumatoid arthritis. To ascertain whether the degree of anaemia present on admission was related to the subsequent response to treatment, patients were grouped according to whether they were anaemic (Hb <80 per cent.) or not (Hb 80 per cent. and over). By this standard, 111 patients were classed as anaemic on admission and 171 as non-anaemic.

The changes in functional capacity in the two groups were compared on admission and at follow-up. 27 per cent. of the anaemic group and 40·9 per cent. of the others were in Grade II of functional capacity on admission. At the time of discharge 69·4 per cent. of the anaemic group and 80·7 per

cent. of the others were in Grades I and II. At follow-up 64·9 per cent. of the anaemic group remained in Grades I and II, in comparison with 77·8 per cent. of the others. The changes in functional capacity in the two groups do not differ significantly.

With regard to the general assessment of improvement, 65·8 per cent. of the anaemic group and 73·6 per cent. of the others were considered to show marked or moderate improvement. This difference is not statistically significant.

When improvement in grades of functional capacity was taken as the measure of progress, 55 per cent. of the anaemic group and 63·7 per cent. of the remainder had improved by one or more grades. Again, this difference is not statistically significant.

When a haemoglobin level of under 85 per cent. was used as an indication of anaemia there was no change in the pattern of results. On the other hand, in patients with an initial haemoglobin level of under 65 per cent., response to treatment was much less satisfactory, but the small number of patients (24) with anaemia of this severity invalidated statistical comparison.

It would appear that although cases with a moderate degree of anaemia on admission are capable of as good a response to treatment as those without significant anaemia, the latter were less severely incapacitated initially and throughout the period of observation. In patients with a more severe degree of anaemia on admission the response to treatment was poor.

Erythrocyte Sedimentation Rate on Admission and Discharge.—The E.S.R. on admission was considered in relation to the general assessment of progress made at follow-up. Of 58 patients with a rate of 20 mm./hr or less, 69 per cent. showed moderate or marked improvement, and 14·3 per cent. had deteriorated. Of 152 patients with rates between 20 and 60 mm./hr, 71 per cent. showed moderate or marked improvement and 16·1 per cent. had deteriorated. Of 72 patients with rates over 60 mm./hr, 72·2 per cent. showed moderate or marked improvement and 20·8 per cent. had deteriorated. In view of the unexpectedly good results in patients with a high E.S.R. on admission, the 72 were divided into those admitted to hospital within one year of onset (28) and those with disease of longer duration (44). It was found that of the 28 cases admitted within one year, 83·7 per cent. had been assessed as showing a moderate or marked improvement, whereas only 63·6 per cent. of the remaining 44 had improved to the same extent.

The general assessment of improvement at follow-up was compared with the sedimentation rate on discharge. The number with a rate under 20 mm./hr was 113, of whom 74·3 per cent. showed moderate or marked improvement and 12·4 per cent. were worse. Of 116 patients with rates between 20 and 60 mm./hr, 68·1 per cent. showed moderate or marked improvement and 18·1 per cent. had deteriorated. Of the 53 with rates over 60 mm./hr 67·9 per cent. had improved and 24·5 per cent. had deteriorated.

When the E.S.R. on admission was considered in relation to changes in functional capacity as assessed at follow-up, there was little difference between the three groups in the proportion of cases improved by one or two grades. It is interesting to note, however, that 30·6 per cent. of patients with a rate of over 60 mm./hr on admission improved sufficiently to be moved up two grades. This is in keeping with the previous observation that cases with an acute onset tend to be admitted to hospital at an early stage and to show substantial benefit from treatment.

It would appear that an erythrocyte sedimentation rate over 60 mm./hr is of graver prognostic significance in patients with disease of longer duration than it is in those admitted to hospital within a year of the onset of symptoms. Unless the duration of the disease is taken into consideration, the E.S.R. on admission to hospital is of little value in predicting the ultimate results of treatment in an individual patient.

Discussion

Accurate evaluation of any regime of treatment used in rheumatoid arthritis is rendered very difficult by the lack of information on the natural history of the untreated disease. It is ethically impossible to acquire such information by the study of a large enough group of patients denied all forms of treatment over a period of years. Simple conservative measures, although in themselves unlikely to alter the course of the disease, may significantly influence its effects on the patient. Early application of splints to affected joints may prevent serious impairment of function, or even complete crippledom, without altering the underlying disease process. A clear distinction must be drawn between those forms of treatment, such as gold, which are used in the hope that they will diminish the activity of the disease, and those whose sole aim is the conservation or restoration of function in the affected joints. The value of such simple conservative measures may have been under-estimated in the past. Judged by the results obtained in a recent trial designed to compare the value of cortisone and

aspirin in the treatment of early cases of rheumatoid arthritis (Report by the Joint Committee of the M.R.C. and Nuffield Foundation, 1954), aspirin is as effective as cortisone in maintaining the functional level and controlling the activity of the disease in such patients when both are combined with a simple regime of splints and physiotherapy. At the end of 1 year of treatment the disease was judged to be inactive or only slightly active in 75 per cent. of the patients, and 40 per cent. were regarded as capable of normal work and activity in both groups. It is important to remember, however, in assessing the significance of these results, that the prognosis in patients admitted to hospital within 1 year of the onset of the disease, is very much better than it is in patients coming under treatment for the first time at a later stage. This is borne out in the present study, and further reference will be made to this point later. The application, over a term of years, of simple conservative measures leads to satisfactory results in some 50 per cent. of patients (Short and Bauer, 1948; Ragan, 1949). Results in the present study show that some 70 per cent. of patients showed moderate or marked improvement in their general clinical condition at the end of an average period of 2 years from their discharge from hospital. The proportion of cases in the upper two grades of functional capacity had risen from 35·4 per cent. (all in Grade II) on admission, to 72·4 per cent. at the last follow-up examination. Disease activity decreased substantially following treatment in hospital and this was maintained during the follow-up period. These results compare very favourably with those reported by other workers after the use of gold.

Short (1942) reviewed the gross results reported by various authors. Of 1,800 cases, 63 per cent. showed marked improvement; in 13 per cent. the disease was apparently arrested.

Ragan and Tyson (1946) reported both the immediate response and the results after 3 or 4 years in 142 patients, summarized as follows: Of patients receiving one or two courses of gold, 10 to 20 per cent. can be expected to show no improvement, and 40 to 60 per cent. to show striking improvement, but 80 to 90 per cent. of these will relapse within 5 years.

Ragan (1951) reported the results of treatment at the end of 5 years in 143 patients seen in the first 2 years of their disease: 68 were given gold with good end results in 63 per cent.; 75 received no gold, and in 70 per cent. the end result was good.

The period of follow-up in the present series is too short to allow of strict comparison with these reports, but it would appear that, although temporary remissions in disease activity can be induced by the administration of gold, these cannot be maintained in the majority of cases. In view of the danger of toxic effects and the good response to conservative treatment, little appears to be gained by the administration of gold to patients suffering from rheumatoid arthritis, as the natural course of the disease, when viewed over a term of years, does not appear to be materially altered for the better.

As has already been mentioned, cortisone has proved no more effective than aspirin in the treatment of early cases. It remains to be shown whether its use in cases of longer duration will prove advantageous.

When the medical assessment of improvement in functional capacity is checked against the actual day-to-day activities of patients at home and at work as reported at follow-up examination, there appears to be good correlation. This has been a reassuring feature of the present study, for assessments of improvement in the purely medical aspects of a disease often have little relationship to what the patient is actually able to do.

There appeared to be a close relationship between improvement in health and functional capacity and betterment in social circumstances as assessed by the medical social worker at follow-up. Much of the success of social and economic rehabilitation in these patients could be directly attributed to action taken on their behalf by the medical social worker during and after their stay in hospital. There is no doubt in our minds that the services of a skilled medical social worker, keenly interested in the particular problems of crippled patients and with sufficient time to study their needs, are of inestimable value. Much of the improvement following medical treatment can only be maintained and consolidated if such help is constantly available. Whenever possible patients must be restored to economic as well as physical independence. Long periods of idleness after fitness for work has been restored have a most demoralizing effect on potential wage-earners. In terms of re-employment and the maintenance or improvement of earning capacity, results in the present study have been reasonably satisfactory. In only five instances among 282 patients had the family income fallen between discharge from hospital and the last follow-up examination.

With regard to the type of employment, it is of interest to note that the results of treatment in patients previously employed in work requiring heavy or medium physical effort were somewhat better than in former sedentary workers. It has been suggested that physical rehabilitation may be easier in patients accustomed to fairly strenuous activity.

Of the various factors which may be significant in predicting the response to treatment, the age at the onset of the disease did not appear to be of great importance in the present study.

With regard to sex, the immediate response to treatment in males and females differed little, but assessment at follow-up revealed a striking change in distribution of the sexes over the four grades of functional capacity. In proportion, nearly twice as many males were placed in Grade I, and double the number of women were placed in the two lower grades. The same trend is revealed in the assessment of disease activity at follow-up. It would appear that a higher proportion of males continue to improve after discharge from hospital. This is in agreement with the findings of Short and Bauer (1948), and Bywaters and Dresner (1952), that the prognosis is materially better in males than in females. It would appear, however, that when patients are admitted to hospital within 1 year of the onset of symptoms subsequent progress is as satisfactory in females as in males, although a more prolonged follow-up will be necessary before this impression can be confirmed.

The most important conclusion reached, on the basis of an analysis of the results of treatment on discharge and at follow-up, is that the immediate prognosis in patients admitted to hospital within 1 year of the onset of symptoms is very materially better than it is in patients coming under treatment at a later stage of the disease. This is in general agreement with the findings of other workers. In considering the significance of the striking difference in the response to treatment between cases admitted to hospital early in the disease and those of longer duration, it must be borne in mind that many cases of rheumatoid arthritis run a relatively mild course and prolonged remissions are not uncommon. There is no means at present of distinguishing such cases during the early stages of the disease from others with a graver prognosis. Admission of a significant number of such cases would undoubtedly exert a favourable influence on the pattern of response. All that can be said at this stage is that, in the judgment of the physicians concerned, the patients admitted at an early stage in the disease, all of whom had been under observation as out-patients, appeared to be in urgent need of treatment in hospital. This may be of more significance when it is realized that, in a unit with a limited number of beds, the milder type of case is usually maintained on out-patient treatment so long as clinical progress is reasonably favourable.

As has already been indicated, it was found that all patients with an acute onset and who ran a progressive course had been admitted to hospital within the first year. Their response to treatment was remarkably good and improvement was maintained in the majority throughout the period of follow-up. When their progress was compared with that of the other patients admitted in the first year, they appeared to fare a little better, although the difference did not reach the level of statistical significance. These results suggest that an acute onset may signify a better immediate prognosis than is the case when symptoms and signs appear more insidiously. More detailed study of patients with this type of onset should prove of considerable interest. Their excellent progress both during and after treatment in hospital may indicate that signs of a marked systemic disturbance at the onset occur in cases destined to run a relatively benign course, whether or not they undergo treatment in hospital.

The symmetry or otherwise of the distribution of affected joints on admission did not appear to be of importance, but a longer period of observation may reveal differences not obvious at the present time.

As would be expected, the degree of disability on admission was an important factor in determining the response to treatment. Those with moderate impairment responded much more satisfactorily than those in whom disability was marked, emphasizing once more the need for the institution of treatment before irreversible damage has taken place in many joints.

The haemoglobin level on admission proved to be of little value in predicting the response to treatment, although the small group of patients with levels below 65 per cent. on admission did badly. Similarly, the erythrocyte sedimentation rate and the assessment of disease activity on admission were of little help, although in cases of long duration associated with a marked degree of disease activity on admission, the immediate prognosis was poor. As already indicated, a high E.S.R. in cases with an acute onset admitted within the first year was not of serious significance.

Summary

The objects of this study were to assess the immediate results of treatment in hospital on patients with rheumatoid arthritis; to ascertain how long improvement could be maintained after discharge; to determine the relationship between clinical progress and changes in social and economic status, and to obtain information about factors which might help to predict the likely response to treatment of individual patients. The original group consisted of 307 patients admitted to hospital between

June, 1948, and July, 1951. 282 of this group were available for assessment at the last follow-up examination. Certain broad conclusions have been reached:

(1) The admission to hospital of patients with rheumatoid arthritis is followed in the majority of cases by a substantial improvement in functional capacity and a significant decrease in the activity of the disease.

(2) Improvement is well maintained after discharge, although a more prolonged follow-up is required before it can be claimed that the natural course of the disease has been significantly altered.

(3) A close relationship exists between improvement in the medical sense and betterment of social and economic circumstances.

(4) When skilled advice and help are available, increase in functional capacity leads to increased efficiency at home and at work.

(5) In predicting the immediate response to treatment and the subsequent course of the disease, the most important single factor appears to be the duration of symptoms before admission to hospital. Patients admitted within one year of onset respond very satisfactorily to the basic regime of treatment and the majority continue to improve after discharge. However, results at this stage of the disease may be favourably influenced by the admission of a proportion of patients in whom it is destined to run a relatively benign course.

(6) An acute onset followed by a rapidly progressive course in the early stages may indicate a rather benign form of the disease.

(7) The erythrocyte sedimentation rate and the level of disease activity on admission have little bearing on prognosis.

(8) A mild or moderate degree of anaemia on admission is not of grave significance, but when anaemia is more severe, response to treatment is less satisfactory.

(9) Detailed social and medical supervision may play a fundamental part in consolidating the benefits of hospital treatment. The medical social worker occupies a key position in the organization of long-term care and follow-up.

(10) The results which follow the conscientious application of conservative forms of treatment in hospital compare favourably with those claimed for other forms of treatment, such as the administration of gold or cortisone.

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Aspects médicaux et sociaux du traitement de l'arthrite rhumatismale avec mention particulière des facteurs concernant le pronostic

RÉSUMÉ

Cette enquête sur des malades atteints d'arthrite rhumatismale avait pour but de: évaluer les résultats immédiats du traitement hospitalier; déterminer combien de temps après le renvoi de l'hôpital l'amélioration peut être soutenue; déterminer le rapport entre le progrès physique et les changements des conditions sociales et économiques; et obtenir des renseignements sur les facteurs qui permettraient d'anticiper la réponse individuelle au traitement. Le groupe original consistait de 307 malades hospitalisés entre juin, 1948 et juillet, 1951; 282 d'entre eux ont été suivis et évalués au dernier examen. On est arrivé à quelques simples conclusions:

(1) L'hospitalisation des malades atteints d'arthrite rhumatismale est accompagnée dans la plupart des cas d'une amélioration sensible de la capacité fonctionnelle et d'une diminution appréciable de l'activité morbide.

(2) L'amélioration persiste bien après le renvoi, quoique une observation plus longue serait nécessaire pour pouvoir dire que l'évolution naturelle de la maladie ait été appréciablement modifiée.

(3) Il existe un rapport étroit entre l'amélioration dans le sens médical et celle des conditions sociales et économiques.

(4) Bien avisé et habilement secouru, le malade dont la capacité fonctionnelle est augmentée devient plus efficace chez lui et au travail.

(5) En prédisant la réponse immédiate au traitement et l'évolution ultérieure de la maladie, de tous les facteurs particuliers la durée des symptômes avant l'hospitalisation semble être le plus important. Les malades qui entrent au cours de la première année de leur maladie réagissent très bien au régime essentiel de traitement et la plupart d'entre eux continue à progresser après la sortie. A cette période de la maladie, cependant, les résultats pourraient être favorablement influencés par l'hospitalisation d'un certain nombre des cas destinés peut-être à une évolution relativement benigne.

(6) A la période initiale, un début aigu et une évolution rapide peuvent indiquer qu'il s'agit d'une forme bien benigne de la maladie.

(7) La vitesse de la sédimentation érythrocytaire et l'intensité morbide au moment de l'hospitalisation ont peu d'importance pronostique.

(8) Une anémie légère ou modérée à l'entrée n'importe pas beaucoup, mais lorsqu'elle est plus sévère le malade réagit moins bien au traitement.

(9) La surveillance médicale et sociale scrupuleuse peut jouer un rôle essentiel dans la consolidation des

avantages du traitement hospitalier. L'assistant social sanitaire assume la position principale dans l'organisation des soins post-hospitaliers à long terme.

(10) Les résultats de l'application consciencieuse des méthodes conservatrices de traitement hospitalier ne cèdent en rien à ceux revendiqués pour d'autres méthodes, telles que l'administration de sels d'or ou de cortisone.

Aspectos médicos y sociales del tratamiento de la artritis reumatoide, con mención especial de los factores que afectan el pronóstico

SUMARIO

Se han estudiado enfermos con artritis reumatoide con el objeto de: valorar los resultados inmediatos del tratamineto hospitalario; averiguar cuanto tiempo permanece la mejoría después de la alta; determinar la relación entre el progreso clínico y los cambios de las condiciones sociales y económicas; hallar los factores que permitan anticipar la reacción probable de enfermos individuales al tratamiento. El grupo original consistía de 307 enfermos hospitalizados entre el junio de 1948 y el julio de 1951; de estos, 282 se han podido seguir y examinar en la última valoración. Se ha llegado a algunas conclusiones generales:

(1) La hospitalización de enfermos con artritis reumatoide conduce, en la mayoría de los casos, a una mejoría apreciable de la capacidad funcional y a un regreso marcado de la actividad mórbida.

(2) La mejoría permanece bastante bien después de la alta, aunque un período de observación más largo sería necesario para poder afirmar que el curso natural de la enfermedad haya sido apreciablemente modificado.

(3) Hay relación estrecha entre la mejoría en el sentido médico y la de las condiciones sociales y económicas.

(4) Provisto de consejo y ayuda pericial, el enfermo con su capacidad funcional aumentada se vuelve más eficaz en su casa y en su trabajo.

(5) Para anticipar el resultado cercano del tratamiento y el curso ulterior de la enfermedad, la duración de los síntomas antes de la baja parece el factor particular mas importante. Los enfermos hospitalizados en el primer año de dolencia responden muy bien al régimen básico de tratamiento y en la mayoría de ellos el curso favorable sigue después de la alta. Hay que tomar en cuenta, sin embargo, que en este período de la enfermedad algunos habrían podido tener una evolución benigna también sin hospitalización.

(6) En el período inicial, el comienzo agudo y la evolución rápida pueden indicar que se trata de una forma bastante benigna de la enfermedad.

(7) La velocidad de la sedimentación eritrocitaria y la intensidad de la actividad mórbida en el momento de la baja tienen poca importancia prognóstica.

(8) Una anemia leve o moderada al tiempo de la baja tiene poca importancia pero con una anemia más grave la respuesta al tratamiento es peor.

(9) La vigilancia médica y social escrupulosa puede desempeñar un papel fundamental en la consolidación de los beneficios del tratamiento hospitalario. El asistente médico domiciliario es el pivote en la organización de la vigilancia y de los cuidados posthospitalarios lejanos.

(10) Los resultados de la aplicación escrupulosa de métodos conservadores de tratamineto hospitalario no son inferiores a los reivindicados para otros métodos, tales como la crisoterapia o el tratamiento por la cortisona.

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RHEUMATOID ARTHRITIS IN MALES

AN EPIDEMIOLOGICAL STUDY OF A WELSH MINING COMMUNITY

BY

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Caplan (1953) suggested for the first time in Great Britain that some cases of rheumatoid arthritis amongst coalminers with pneumoconiosis can be recognized from a characteristic chest *x*-ray appearance. An epidemiological investigation of this new syndrome showed that this nodular lung fibrosis (Fig. 1, opposite), was associated with rheumatoid arthritis in more than 50 per cent. of cases; it also suggested that the prevalence of rheumatoid arthritis was increased amongst men with complicated pneumoconiosis (Miall and others, 1953).

To determine whether the progressive massive fibrosis (P.M.F.) of complicated pneumoconiosis was an aetiological factor in the development of the arthritis, a survey of rheumatoid arthritis was undertaken in a Welsh mining valley where P.M.F. was known to be common amongst the miners. This paper describes further investigations into the relationship between rheumatoid arthritis and pulmonary disease.

A previous *x*-ray survey of the Rhondda Fach had shown that the prevalence of massive fibrosis rose from over 10 per cent. in the 35-39 age group to over 20 per cent. in the 65+ age group (Cochrane and others, 1952), and the present survey was therefore carried out during the "follow-up" chest *x*-ray survey of the Rhondda Fach, undertaken by the M.R.C. Pneumoconiosis Research Unit and the Welsh Regional Hospital Board during the summer of 1953.

Methods

(1) Preliminary Screening.—The valley population was defined by private census immediately before the *x*-raying started in each town, and during this census a note was made of all individuals said to be suffering from any form of arthritis. 90 per cent. of the complete population over the age of 15 was subsequently *x*-rayed (Cochrane and others, 1955), and each individual as he attended for *x* ray was asked whether he had suffered or was suffering from painful swellings of the small joints of the hands or feet.

Lists of cases of rheumatoid arthritis were provided from the medical practitioners in the valley and from the rheumatism clinic serving the district. From these four sources, supplemented later by information obtained from patients who were found to have rheumatoid arthritis, a list was compiled of individuals with rheumatic complaints; they were visited subsequently by the author, who completed the preliminary screening with a history and brief clinical examination.

(2) Diagnostic Criteria.—In epidemiological surveys it is essential that the findings of different observers should be comparable. Any differences in the results of surveys undertaken by different workers can often be more confidently attributed to the diagnostic standards used than to true differences in the prevalence of disease; especially is this true when assessment is made on subjective evidence alone. Real epidemiological differences are only likely to be found when some objective evidence is incorporated in the diagnostic criteria used, so that direct comparisons can be made.

In this survey, the diagnosis was based upon a characteristic history of a polyarthritis involving peripheral joints, whether residual physical signs were present or absent, supported by *either* radiological evidence of rheumatoid arthritis in the hands or feet, *or* by a positive differential agglutination test (Rose and others, 1948; Ball, 1952). In field survey work a reproducible diagnosis at a rather high level of severity is more valuable than a non-reproducible one at a lower level. Observer error in the interpretation of radiographs of bony structures has been investigated by Kellgren and Lawrence (1952) and shown to be slight. Our previous investigations confirmed that the observer error between two rheumatologists reading films for evidence of rheumatoid arthritis is small (Miall and others, 1953) and a more recent investigation showed that, though the observer error between experienced and inexperienced readers is greater, agreement in the interpretation of *x* rays of the hands and feet was found in 191 of 223 pairs of films. In 91 of these pairs evidence of rheumatoid arthritis was agreed to be present; in one hundred pairs it was agreed to be absent. In 32 films there was disagreement, largely due to the interpretation by inexperienced readers of the changes of generalized osteo-arthritis as rheumatoid arthritis with secondary osteo-arthritis.

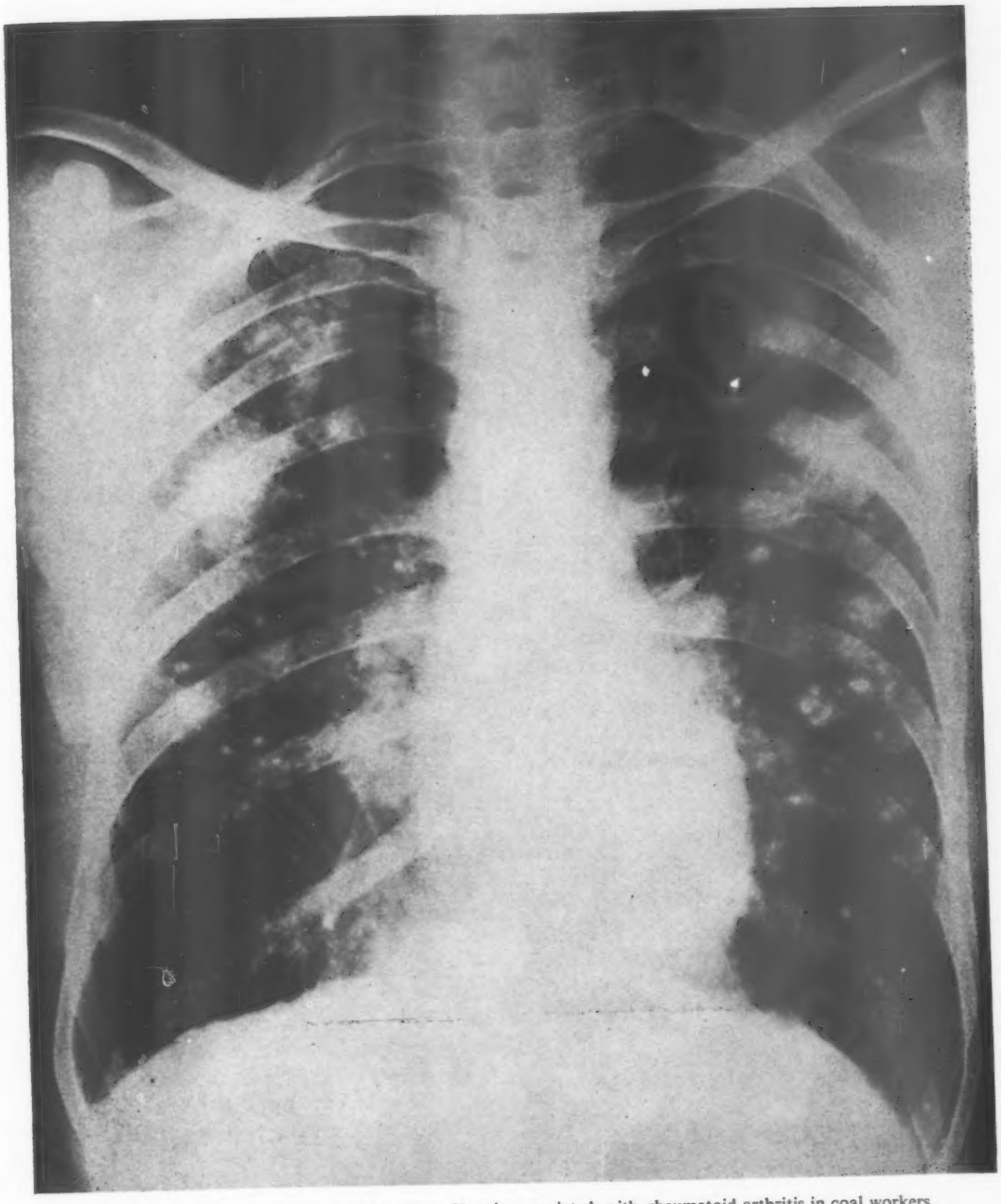

Fig. 1.—Typical example of nodular lung fibrosis associated with rheumatoid arthritis in coal workers.

No evidence is available about variation between laboratories on the results of the differential agglutination test carried out on the same sera, but this is likely to be small provided the same techniques are adopted and the criteria of positivity stated.

It is certain that, by using these rather strict criteria, some cases of rheumatoid arthritis have been missed: monarticular cases, for example, are excluded and also those in which only the larger central joints are involved. In the Empire Rheumatism Council's inquiry into the aetiological factors associated with rheumatoid arthritis (Lewis-Faning, 1950), 532 cases of rheumatoid arthritis of less than 5 years' duration were studied. Although a selected group of hospital in-patients, and therefore not comparable for frequency of symptoms or signs with a complete population of cases of this disease, an analysis

showed that peripheral joints were involved in 98 per cent., so the initial selection of cases on the basis of a history of a peripheral polyarthritis should have excluded few cases of a severity warranting admission to a centre specializing in the treatment of rheumatism. On the other hand, by using these criteria, a number of cases of generalized osteo-arthritis (Kellgren and Moore, 1952) have been rejected, which, from their histories and residual signs, would not have been distinguished from inactive rheumatoid arthritis.

So, with the exception of the bedridden, all who were judged to be possible cases of rheumatoid arthritis were asked to submit to radiological examination of the hands and feet as well as of the chest, and to have a blood test.

(3) Groups Studied

(*a*) *Cases of Arthritis.*—Some information about the total population of 9,430 males over the age of 15 was obtained from the census takers, the general practitioners, and the local rheumatism clinic, but only 8,653 men (92 per cent.) were directly questioned about arthritis.

274 men were interviewed and medically examined, and 78 of these were considered to be cases of rheumatoid arthritis, but only 66 of them satisfied the strict criteria adopted, and these form the group studied in this paper. Of the twelve remaining men, who were considered to be definite or probable cases of rheumatoid arthritis, four had some residual signs, but proof of rheumatoid arthritis was impossible using these criteria. *X* rays were taken of the peripheral joints of seventeen other men, who gave doubtful histories and had either no residual signs or residual signs of generalized osteo-arthritis, and nine of them also had the differential agglutination test performed, but all failed to fulfil the criteria adopted.

The results of the survey amongst females, in whom cases of polyarthritis which do not satisfy these criteria are more common, and a comparison of the prevalence in the two sexes, will be reported later.

(*b*) *Controls.*—For studies of chest *x*-ray abnormalities, industrial histories, and family histories amongst cases of rheumatoid arthritis, it was important to have control groups similar to the rheumatoid group in all respects, except that of rheumatoid arthritis. All data for the complete population of the valley had been transferred to punched cards and these were used for random selection of age-balanced control groups from the appropriate populations of miners and non-miners.

Results

(a) Radiography of Hands and Feet.—Radiographs were taken of the hands and feet of sixty of the 66 cases and of the hands only in one other case. Of the five remaining, three were bedridden, and two refused to have *x* rays taken.

These *x* rays were kindly read by Prof. J. H. Kellgren, who was asked to classify them into four grades: severe, moderate, and slight changes of rheumatoid arthritis, and normal. A set of control bones was used to facilitate the diagnosis of osteoporosis.

20 per cent. of the whole group showed no radiological changes in peripheral joints, and were accepted as cases of rheumatoid arthritis on the basis of their clinical findings, supported by a positive differential agglutination test.

(b) Differential Agglutination Test.—A modification of the Rose agglutination test (Ball, 1950) was used by Dr. J. Ball who has reported the results in greater detail (Ball, 1955). The test was carried out on 64 of the 66 cases and was negative (*i.e.* no agglutination at a dilution of 1 : 4 at 1 hr, or of 1 : 32 at 18 hrs) in ten cases (15 per cent.), who were therefore accepted as cases of rheumatoid arthritis on the basis of their clinical findings supported by *x*-ray changes in the peripheral joints.

(c) Prevalence.—The prevalence of rheumatoid arthritis amongst all males, miners, and non-miners is shown in Table I. Fig. 2 (opposite) compares that amongst miners and non-miners. Because of the small numbers involved, cases have been grouped into 10-year age groups, selected as shown, to give a smooth curve. When analysed in 5-year age groups a significant difference occurs in only the 40-44-year age group ($P = 0{\cdot}04$). Little importance should be attached to a significant difference at this level in only one of the nine 5-year age groups. The overall difference in prevalence between miners and non-miners is not significant; the prevalence of arthritis amongst the non-miners is, however, based

TABLE I

PREVALENCE OF RHEUMATOID ARTHRITIS AMONGST ALL MALES, MINERS AND EX-MINERS, AND NON-MINERS (RHONDDA FACH, 1953)

Age Group (yrs)	All Males			Miners and Ex-Miners			Non-Miners		
	Total	No.	Per cent.	Total	No.	Per cent.	Total	No.	Per cent.
15–19	892	—	—	310	—	—	582	—	—
20–29	1,688	3	0·18	754	1	0·13	934	2	0·21
30–39	1,846	5	0·27	1,204	3	0·25	642	2	0·31
40–49	1,737	17	0·98	1,333	15	1·13	404	2	0·50
50–59	1,470	21	1·43	1,281	18	1·41	189	3	1·59
60+	1,797	20	1·11	1,631	17	1·04	166	3	1·81
Total ..	9,430	66		6,513	54		2,917	12	

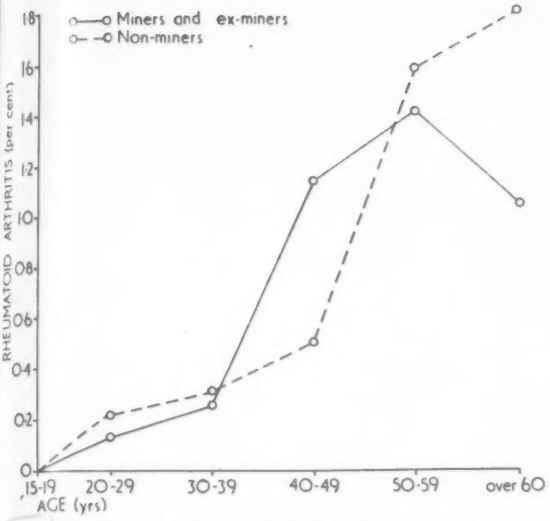

Fig. 2.—Prevalence of rheumatoid arthritis amongst miners and ex-miners and non-miners (Rhondda Fach, 1953).

on only twelve cases, whereas there were 54 cases amongst miners and ex-miners.

The similarity in the prevalence of arthritis between the mining and non-mining male populations, in spite of the very high prevalence of massive fibrosis amongst the miners, suggests that complicated pneumoconiosis is unlikely to be of *aetiological* importance in this disease.

(d) Relationship with Pulmonary Disease

(*i*) *Miners and Ex-Miners.*—Full-size chest radiographs were taken of all the 54 miners and of ten of the twelve non-miners with rheumatoid arthritis.

Table II shows the chest *x*-ray results in the miners with arthritis compared with those of an age-balanced control group selected at random from those without arthritis. It must be remembered that, in this area, 50 per cent. of the miners and ex-miners over the age of 35 show some radiological abnormality.

It is, nevertheless, striking that only thirteen of the 54 arthritics (24 per cent.) had normal *x* rays compared with 24 of the 54 controls (44 per cent.), and whereas 25 of the rheumatoid arthritis cases (46 per cent.) showed massive fibrosis, this condition was present in only ten of the control group (19 per cent.). There was also a slight increase in the amount of active or inactive post-primary tuberculosis in the rheumatoid arthritis group—ten cases as compared with six in the controls. For statistical analysis, pleurisy has been grouped with post-primary tuberculosis; applying the usual contingency table test, $\chi^2 = 14{\cdot}14$ with three degrees of freedom, and $0{\cdot}01 > P > 0{\cdot}001$, *i.e.* results as diverse as those shown in Table II would not be expected by chance alone in 1 trial in 100.

The distinction between progressive massive fibrosis and tuberculosis is frequently difficult radiologically. Tuberculous lesions, in the presence of simple pneumoconiosis, may retain all the radiological features of tuberculosis, but this is not always the case, and every gradation between characteristic tuberculous infiltration and obvious progressive massive fibrosis may be found, so that the distinction between the two is often arbitrary.

The type of nodular lung fibrosis described by Caplan and illustrated in Fig. 1 has only been seen in those who have been exposed to industrial dust inhalation of some kind, though it is not confined to coalworkers. In Belgium, Colinet (1950) described a somewhat similar syndrome in a woman who had been engaged in handling siliceous dusts. Radiologically, in coal-workers, these rounded opacities often develop upon a less severe grade of simple pneumoconiosis than does ordinary massive fibrosis; those in which the background of simple pneumoconiosis is less than Category 2 (International Classification) were routinely read as tuberculosis, whereas those with Category 2 or more were included in the P.M.F. group. The number of cases of Caplan's syndrome coming in these two columns of Table II are indicated in brackets, and together they account exactly for the difference between the rheumatoid and the control groups.

(*ii*) *Non-Miners.*—The chest *x* rays of the non-mining males with arthritis show a similar excess of

TABLE II
COMPARISON OF CHEST RADIOGRAPHS OF MINERS AND EX-MINERS WITH AND WITHOUT RHEUMATOID ARTHRITIS (RHONDDA FACH, 1953)

Group	Progressive Massive Fibrosis		Post-Primary Tuberculosis		Pleurisy		Simple Pneumoconiosis		Normal		Total	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Rheumatoid ..	25 (15)*	46	10 (4)*	19	1	2	5	9	13	24	54	100
Control	10	19	6	11	1	2	13	24	24	44	54	100

* Cases of Caplan's syndrome are indicated in brackets.

TABLE III

COMPARISON OF CHEST RADIOGRAPHS OF NON-MINERS WITH AND WITHOUT RHEUMATOID ARTHRITIS (RHONDDA FACH, 1953)

Group	Post-Primary Tuberculosis		Pleurisy		Normal		Total	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Rheumatoid	4	40	1	10	5	50	10	100
Control	1	5	—	—	19	95	20	100

post-primary tuberculosis over their age-balanced control group, which was double the size and was selected at random from the non-mining male population without rheumatoid arthritis (Table III). Four of the ten showed evidence of post-primary tuberculosis, three of the four being considered to have clinically significant disease; one other showed evidence of pleurisy; in the control group only one case of healed post-primary tuberculosis was noted.

For analysis, pleurisy has again been grouped with post-primary tuberculosis. Although the numbers are small, the association between rheumatoid arthritis and changes in the chest radiographs is again statistically significant ($0{\cdot}05 > P > 0{\cdot}01$).

(e) Heredity in Rheumatoid Arthritis.—An investigation to determine the importance of genetic factors in rheumatoid arthritis was made by enquiring into the presence of the disease in parents and siblings of these cases and comparing them with those of a control group. The inquiry was limited to parents and siblings so that more reliance could be placed upon the data, and where possible the diagnosis was confirmed by visiting secondary cases living near the valley. Where this was impossible, data were obtained by questionnaire. If the affected relative had died or could not be visited, only clear-cut histories were accepted.

Family histories were available for 61 of the 66 men with arthritis: in three cases the relatives were unknown; one refused to co-operate; and the other was living away at the time of this later investigation. Two pairs of brothers occur in this group of 61 cases; to include these four men as index cases would exaggerate the importance of heredity and one of each pair has been omitted. This study is therefore based upon 59 rheumatoid arthritis index cases and 89 index controls, of the same age as the arthritics, who were selected at random from the inhabitants of the valley (Table IV).

Histories were available for 110 parents and 244 siblings of the 59 index cases, and for 168 parents and 334 siblings of the 89 controls (over 90 per cent. of the relatives of controls who were living in the valley were also examined).

The family sizes were very similar in the two groups; the mean ages of the parents differed by less than 1 year, the mean age of the siblings was 4 years greater in the control group.

Amongst the 354 relatives of index cases, eleven secondary cases were found (3·1 per cent.). These occurred in eight families. In each of five of these families two cases of rheumatoid arthritis were found, in each of the other three families there were three cases; eight of the eleven secondary cases were confirmed by visiting, the remainder by questionnaire. In the 502 relatives of controls, three cases of rheumatoid arthritis were found (0·6 per cent.). These differences are statistically significant.

Stecher and his colleagues (1953) report similar findings in a larger scale investigation in the United States. They investigated the disease in 1,453 parents, siblings, and children of 224 index cases of

TABLE IV

INCIDENCE OF RHEUMATOID ARTHRITIS AMONGST PARENTS AND SIBLINGS OF 59 MALE CASES AND 89 CONTROLS (RHONDDA FACH, 1953)

Index Cases	No.	Parents				Siblings				Parents and Siblings			
		Histories Available	Mean Age (yrs)	Rheumatoid Arthritis	Per cent.	Histories Available	Mean Age (yrs)	Rheumatoid Arthritis	Per cent.	Histories Available	Mean Age (yrs)	Rheumatoid Arthritis	Per cent.
Rheumatoid Arthritis	59	110	63·5	1	1	244	44·3	10	4·1	354	51·4	11	3·1
Control	89	168	64·2	3	2	334	48·3	—	—	502	53·0	3	0·6

Only relatives over the age of 25 years have been considered. For dead relatives, age at death has been used, if over 25 years.

both sexes, and reported 3·1 per cent. of the relatives affected. When the children are excluded the incidence rises to 3·7 per cent., compared with the 3·1 per cent. in the Rhondda Fach. Unfortunately, the data quoted for controls by these authors cannot be directly compared with the Rhondda data, as they included an unstated number of children of index cases. It seems likely, however, that the results of the two surveys are of the same order of magnitude, for Stecher and others report 0·58 per cent. of affected individuals (when control index cases without arthritis are included), compared with 0·51 per cent. for the Rhondda when control index cases are included.

In the Empire Rheumatism Council investigation (Lewis-Faning, 1950) 3·8 per cent. of siblings of rheumatoid arthritics were reported to be affected, compared with 1·8 per cent. of siblings of controls, but the data for arthritis in parents are not restricted to rheumatoid arthritis.

Short and others (1949) reported positive family histories in 11·9 per cent. of patients and 5·1 per cent. of controls. The results of this survey, expressed similarly would be 13·6 per cent. and 3·4 per cent. respectively.

Thus, in spite of the acknowledged weaknesses of this type of investigation due to the greater awareness of affected relatives of patients suffering from the condition, it seems certain that heredity is an aetiological factor of importance in this disease.

(f) **Occupational History.**—In a previous paper (Miall and others, 1953) the duration of exposure to stone dust appeared possibly to be an important factor in the development of Caplan's syndrome. An analysis of the industrial histories of all the miners and ex-miners with rheumatoid arthritis showed that stone-dust exposure occurred no more frequently in them than in an age-balanced control group, and though amongst the rheumatoid arthritics the cases with Caplan's syndrome show a higher proportion with stone-dust exposure, the difference is not statistically significant.

Comparison of Prevalence Data with Other Surveys

There have been few other surveys of rheumatic diseases in complete or randomly sampled communities, and in none have the results of any objective tests used in the diagnosis been published.

In the British Isles, the Newman report (Ministry of Health, 1924) was based upon general practitioners' records for the employed population covered by the National Health Insurance. The rate quoted for men is similar to that found in the Rhondda in the younger age groups, but, as would be expected, the rate in older males is much lower than in the Rhondda.

Nisbet (1946) gives an incidence of 0·17 per cent. in Scottish males over the age of 15 years. Both Nisbet and the Sickness Survey (Stocks, 1949), which quotes a figure of 0·42 per cent. for males and females over the age of 16 (based on self-diagnosis), found a higher prevalence of rheumatoid than osteo-arthritis, a most unusual finding.

A Royal Commission on Rheumatic Diseases in Sweden (1945) estimated that 0·25 per cent. of the total Swedish population was suffering from rheumatoid arthritis during 1943. Kalbak (1953) reported the prevalence amongst in-patients and out-patients and the disabled in Denmark, but in a survey of rheumatism in the general population, no breakdown by type of disease is published.

De Blécourt and Basart (1953), on a sampling basis, found 0·81 per cent. of males over the age of 13 with rheumatoid arthritis in Holland.

Kellgren and his colleagues (1953) found a higher prevalence than any of these other workers, but his survey was carried out in Lancashire, where, according to the Newman report, all types of rheumatism are increased. Kellgren reports 1·7 per cent. amongst males, based on complaints within the preceding 5 years.

The prevalence of rheumatoid arthritis cases which satisfy the strict criteria used in this survey amongst males over the age of 15 years in the Rhondda is found to be 0·7 per cent.

Discussion

This survey of rheumatoid arthritis amongst males living in a Welsh mining valley was designed to study the relationship between that disease and pulmonary abnormalities. In particular, it was important to determine whether massive fibrosis was responsible for an increase of rheumatoid arthritis in miners; it had already been shown that the prevalence of this type of arthritis was high amongst cases of massive fibrosis. The survey showed that though the prevalence of rheumatoid arthritis amongst all cases of massive fibrosis is about 2·7 per cent., compared with 0·6 per cent. amongst miners without massive fibrosis, the prevalence of the disease in miners does not differ significantly from that amongst non-miners, and therefore it is most unlikely that massive fibrosis is in any way predisposing to rheumatoid arthritis.

The difference in the shape of the two curves shown in Fig. 2, though not statistically significant, may represent an epidemiological difference which would have been significant had the numbers been

greater. An analysis by age at onset might have thrown further light on any difference between the two groups; such an analysis, however, is impossible, as in the past there have been few opportunities for occupation other than mining, so that most cases in which there is a late onset of arthritis fall into the mining group.

The attack rate of rheumatoid arthritis, as deduced from the prevalence data, is considerable, and our findings, which are in agreement with those of Stecher and others (1953) and Lewis-Faning (1950), show that more than 50 per cent. occurs over the age of 40 years. Death rates, as quoted by the Registrar-General (Brooke, 1952), are extremely low, less than 20 per million living. With this sustained attack rate over the age of 40 and this low mortality rate, we should expect the prevalence rate to increase steadily at least to the age of 60 years, as it appears to do in the non-mining males. The shape of the prevalence curve for miners and ex-miners can be explained by an increasing attack rate or by an increased mortality rate (or an increased migration rate from the valley) in men with arthritis. The data are insufficient to explain which, if any, of these three factors is operating.

Almost half the patients with rheumatoid arthritis amongst miners show massive fibrosis (46 per cent.), and a further 19 per cent. show evidence of post-primary tuberculosis; the corresponding figures are 19 per cent. and 11 per cent. in the control group of miners without arthritis.

As the excess of tuberculosis and massive fibrosis in the miners disappears when cases of Caplan's syndrome are excluded, it could be argued that this is evidence that such cases are of a different aetiology, but no other evidence supports such a view. It is possible that this is so; more than one type of inflammatory focus in dust-laden lungs may initiate massive fibrosis.

Much evidence suggests that complicated pneumoconiosis is a tuberculous condition (Rogers, 1946; Fletcher and Gough, 1950; Van Mechelin, 1953; James, 1954). There are no pathological features to suggest a different aetiology for Caplan's syndrome, and, in fact, two of the 32 cases which have been fully investigated as in-patients, have had tubercle bacilli in the sputum.

If we accept as a working hypothesis that complicated pneumoconiosis is a modified form of tuberculosis, and that Caplan's syndrome is a modification of complicated pneumoconiosis, we must seek some explanation of this difference in the amount of chest *x* ray abnormalities between rheumatoid arthritics and other men.

It appears probable that massive fibrosis and tuberculosis are not of *aetiological* importance in rheumatoid arthritis. We must therefore postulate that patients with rheumatoid arthritis are more liable to show radiological changes of this kind than normal people. If this is true, is the difference one of environment or one of tissue response?

There is no evidence to suggest that environmental factors are responsible; there is, however, some evidence to suggest an abnormal tissue response in some cases of rheumatoid arthritis.

It has already been shown that hereditary factors are of importance in rheumatoid arthritis. Whatever factors comprise the rheumatoid diathesis, one may be associated with an altered tissue response to infections.

That there is an altered tissue reaction in the lungs in at least some cases of rheumatoid arthritis is suggested by Caplan's syndrome itself. Furthermore, in studying this syndrome, we find cases in which the lung lesions precede the onset of arthritis by several years, and conversely others in which they develop several years after its onset. This fact alone is difficult to explain except in terms of some altered tissue reaction in those liable to rheumatoid arthritis.

This concept is supported also by the finding of three cases of Caplan's syndrome in one family: a father and two of his three sons.

In our enquiry into the familial incidence of rheumatoid arthritis, additional cases were found in 13·6 per cent. of families. One purpose of this inquiry was to see whether those miners with the Caplan type of chest *x*-ray appearance but without arthritis had a similar familial incidence of rheumatoid arthritis, and this seems to be so; seventeen such cases have been seen and in two of them parents or siblings had been affected (12 per cent.).

Any attempt to explain the chest *x*-ray findings reported here must be speculative. It has been demonstrated by Kettle (1934) and more recently by Attygalle and others (1954) that the degree of fibrosis produced by the intra-tracheal injection of a combination of dust and killed avirulent tubercle bacilli (B.C.G.) in experimental animals is greater than that obtained by either of these agents alone. If a similar synergic process occurs in man this might explain the lack of reported cases resembling Caplan's syndrome in those with no history of exposure to dust inhalation; but to account for the characteristic features of Caplan's syndrome and the increased prevalence of radiological opacities found in men with rheumatoid arthritis we must postulate some additional factor peculiar to them.

This additional factor may be associated with an unusual susceptibility to all infections. Cobb and his colleagues (1953) have reported that the causes

of death in rheumatoid arthritis differ from the causes in the general population, and amongst those causes is an increased frequency of infections of all kinds.

But if, as Kellgren (1952) has suggested, the fundamental abnormality in rheumatoid disease involves the disintegration of the collagen-polysaccharide complex of normal connective tissue, it is possible that these radiological findings represent not only the reaction of the lungs to tuberculosis, whether or not it is modified by dust, but also a secondary reaction to changes occurring in the collagen of complicated pneumoconiosis and tuberculosis.

Conclusions

This survey raises again the much discussed relationship between rheumatoid arthritis and tuberculosis. Poncet (1902) first suggested that rheumatoid arthritis could be of tuberculous origin, and many papers since then have appeared with descriptions of cases of rheumatoid arthritis accompanied by active tuberculosis (Copeman, 1936; Sheldon, 1946; Dalgleish, 1952; and others). The literature on this subject has been well reviewed by Brav and Hench (1934). As is stated in Rheumatism and Arthritis: Review of American and English Literature of Recent Years (1953), "There are no convincing data supporting the concept of 'tuberculous rheumatism'."

Though tuberculosis as a cause of rheumatoid arthritis is improbable, the evidence presented here suggests that a relationship between the two diseases may exist and that this relationship is due to some alteration in tissue reaction which is often of genetic origin and perhaps a component of the so-called "rheumatoid diathesis".

Summary

(1) An epidemiological survey of rheumatoid arthritis in a complete community of 9,430 males over the age of 15 years has been carried out in South Wales to determine the relationship between this disease and pulmonary abnormalities.

(2) All cases found were asked to submit to *x* rays of chest, hands, and feet, and to a differential agglutination test; criteria confirmed by objective evidence were used in the diagnosis of rheumatoid arthritis.

(3) No increased prevalence of rheumatoid arthritis was found amongst miners and ex-miners in this community where progressive massive pulmonary fibrosis and cases of Caplan's syndrome are prevalent. It is concluded, therefore, that neither exposure to dust nor the lung changes of complicated pneumoconiosis are of any aetiological importance in the disease.

(4) A significantly high prevalence of massive fibrosis and tuberculosis was found amongst the miners with arthritis, and a significantly high prevalence of tuberculosis was found amongst the non-miners.

(5) We have confirmed the findings of others that inheritance is of importance in the aetiology of this disease. This is also true of Caplan's syndrome and of cases found with the characteristic Caplan chest *x* ray without arthritis.

(6) Caplan's syndrome and the present findings suggest an inherited abnormality of tissue reaction, not confined to the skeletal system, in those with, or presumably liable to develop, rheumatoid arthritis.

(7) This hypothesis would account for the numerous descriptions of cases of rheumatoid arthritis accompanied by active tuberculosis which have appeared since Poncet described tuberculous rheumatism in 1902, but it does not confirm Poncet's view that tuberculosis is a cause of rheumatoid arthritis.

This survey depended upon the active co-operation of many disabled people in the Rhondda Fach, and I should like to record my thanks to them and to the many others who so willingly helped in this work.

Assistance was given by Dr. A. Caplan, of the Pneumoconiosis Medical Panel, Cardiff, and by my colleagues at the Pneumoconiosis Research Unit. In particular, Dr. J. C. Gilson, the Director, and Dr. A. L. Cochrane gave much helpful criticism and advice, Mr. R. G. Carpenter undertook the statistical analysis, and the Unit's epidemiological and radiological teams carried out much of the field work involved.

It is a pleasure to acknowledge my indebtedness also to Prof. J. H. Kellgren who gave invaluable advice and kindly read the *x* rays of the peripheral joints, to Dr. J. Ball who undertook the differential agglutination tests, to Drs. A. L. Cochrane and V. H. Springett who read the chest *x* rays, and to Dr. J. F. Brailsford who also gave radiological advice. Dr. Griffith Jones kindly provided information about a number of patients under his care.

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Arthrite rheumatismale chez le mâle
Etude épidémiologique d'une communauté minière galloise

RÉSUMÉ

(1) On a procédé a une étude épidémiologique de l'arthrite rhumatismale dans une communauté complète des Galles du Sud chez 9.430 mâles âgés de plus de 15 ans pour déterminer le rapport entre cette maladie et les anomalies pulmonaires.

(2) On a demandé à tous les cas décélés de se soumettre à la radiologie des poumons, des mains et des pieds et à la réaction d'agglutination différencielle; pour le diagnostic d arthrite rhumatismale on s'est imposé des critères déterminés confirmés par des preuves objectives.

(3) On n'a pas trouvé que la fréquence d'arthrite rhumatismale soit exagérée chez les mineurs et les anciens mineurs de cette communauté, dans laquelle la fibrose pulmonaire massive et progressive et le syndrome de Caplan se voient si souvent. On en conclut, que l'exposition à la poussière et les altérations pulmonaires compliquant la pneumoconiose ne constituent pas un facteur étiologique important de la maladie rhumatismale.

(4) On a trouvé que la fibrose massive et la tuberculose étaient appréciablement plus fréquentes chez les mineurs atteints d'arthrite et une prédominance appréciable de la tuberculose s'est observée chez les non-mineurs.

(5) Nous avons confirmé les résultats des autres que l'hérédité joue un rôle important dans l'étiologie de cette maladie. Il en est de même pour le syndrome de Caplan, avec son image radiologique pulmonaire caractéristique, même sans arthrite.

(6) Le syndrome de Caplan et les résultats obtenus ici suggèrent l'existence d'une anomalie héréditaire de la réaction tissulaire qui, chez les rhumatisants ou ceux susceptibles de le devenir, ne se limite pas au système ostéo-cartilagineux.

(7) Cette hypothèse expliquerait les cas d'arthrite rhumatismale associée à la tuberculose évolutive, si souvent rapportés depuis que Poncet (1902) a décrit le rhumatisme tuberculeux, sans toutefois confirmer l'opinion de Poncet que la tuberculose soit la cause de l'arthrite.

Artritis reumatoide en el hombre
Estudio epidemiológico de una comunidad minera galesa

SUMARIO

(1) Se estudió la epidemiología de la artritis reumatoide en una comunidad completa de las Gales de Sur en 9.430 hombres de más de 15 años de edad para determinar la relación entre esta enfermedad y las anomalías pulmonares.

(2) Se pidió a todos los casos descubiertos que se sometieran a la radiología del pecho, de las manos y de los pies, así como a la reacción de aglutinación diferencial. Para el diagnóstico de la artritis reumatoide se impuso criterios determinados confirmados por hechos onjetivos.

(3) No se halló frecuencia exagerada de artritis reumatoide en los mineros o antiguos mineros de esta comunidad, en la cual la fibrosis pulmonar masiva y progresiva y el sindrome de Caplan abundan. Se concluye que la exposición al polvo o alteraciones pulmonares complicando la pneumoconiosis no constituyen un factor etiológico importante en la enfermedad reumática.

(4) Se halló que la fibrosis masiva y la tuberculosis fueron significativamente más frecuentes en mineros con artritis mientras que en los que no eran mineros hubo preponderancia de la tuberculosis.

(5) Confirmamos los resultados de otros autores que la herencia juega un papel importante en la etiología de esta enfermedad. Esto es aplicable al síndrome de Caplan con su cuadro radiológico pulmonar característico, aún sin artritis.

(6) El síndrome de Caplan y los resultados obtenidos aquí sugieren una anomalía hereditaria de la reacción de los tejidos que en sujetos reumáticos o con terreno reumático no se limita al sistema óseo-cartilaginoso.

(7) Esta hipótesis explicaría los casos de artritis reumatoide asociados a la tuberculosis activa, relatados en gran número desde que Poncet (1902) había descrito el reumatismo tuberculoso, sin confirmar la opinion de Poncet que la tuberculosis sea la causa de la artritis.

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DIFFERENTIAL AGGLUTINATION TEST IN RHEUMATOID ARTHRITIS COMPLICATED BY PNEUMOCONIOSIS

BY

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During a survey of rheumatoid arthritis in a South Wales mining valley (Miall and others, 1953; Miall, 1955), the differential agglutination test (D.A.T.) was adopted as one of the diagnostic criteria of this syndrome. One of the principal objects of the survey was the further investigation of the observation of Caplan (1953) of an association between an unusual form of progressive massive pulmonary fibrosis (P.M.F.) and rheumatoid arthritis; the serological data obtained during the survey are presented here and discussed with particular reference to this problem of the association of pulmonary disease and rheumatoid arthritis in miners.

Methods

The technique used in performing the D.A.T. has been previously described (Ball, 1950). In the present study a serum was accepted as positive if agglutination to a titre of 1 : 32 or more was observed when the test was read after 18 hrs. The sensitivity of the test was kept constant by using a series of human sera of known agglutinating activity as standards with which the appropriate dilution of different batches of anti-sheep rabbit serum could be determined.

The cases of rheumatoid arthritis were divided into three types according to the following clinical and radiological data provided by Dr. W. E. Miall.

Type 1.—Cases with a characteristic clinical history, definite residual clinical signs, and radiological evidence of rheumatoid disease.

Type 2.—Cases with a characteristic history and residual signs but with no definite radiological abnormality.

Type 3.—Cases with a characteristic history but with neither residual symptoms, signs, or radiological abnormality.

These criteria are less strict than those adopted in the epidemiological studies (Miall, 1955) and probably allow the inclusion of some doubtful cases. Serological and chest *x*-ray findings were available for all but three of the 78 cases of rheumatoid arthritis detected in the survey. Among the 75 cases accepted for analysis, *x* rays of the limbs were not available in three; two of these had P.M.F. and were bed-ridden with rheumatoid arthritis and have therefore been accepted as Type 1 cases. The remaining case had a Caplan chest *x* ray and a characteristic history of rheumatoid arthritis, but the residual signs of this disease were limited to one elbow; this case was placed in the Type 2 group.

Results

The D.A.T. results in the 75 cases are presented in Table I according to the chest *x*-ray findings and the clinical type of rheumatoid arthritis. There is suggestive evidence in this table that among cases of either Caplan's syndrome, P.M.F., or tuberculosis positive tests will be observed more frequently than in cases with either a normal chest or with simple pneumoconiosis.

Previous work has shown that the results obtained with the D.A.T. are positively correlated with the severity and duration of the arthritis and with the presence of subcutaneous nodules. A comparison of the arthritis in the various chest disease groups was made by assessing the severity of the disease according to the proportion of Type 1 cases and the duration of the disease according to the proportion of cases with a duration of over 3 years respectively. To facilitate analysis, the combined normal and simple pneumoconiosis cases have been grouped for

TABLE I

RELATION OF TEST TO CLINICAL TYPES OF RHEUMATOID ARTHRITIS AND THE CHEST *X*-RAY FINDINGS

Clinical Type of Rheumatoid Arthritis	Chest *X*-Ray Findings										Total No. of Cases
	Normal		Simple Pneumoconiosis		Tuberculosis		Massive Fibrosis		Caplan's		
	+ve	Total	+ve	Total	+ve	Total	+ve	Total	+ve	Total	
1	8	14	1	3	10	11	9	9	11	12	49
2	2	2	0	1	0	1	1	3	3	3	10
3	1	7	2	2	1	2	0	1	4	4	16
Total	11	23	3	6	11	14	10	13	18	19	75

comparison with cases of tuberculosis and the combined cases of P.M.F. and Caplan's syndrome.

Tables II and III show that, in respect of these features of the arthritis, the normal and simple pneumoconiosis group is closely similar to the P.M.F. and Caplan group; and any differences in the serological results may therefore be reasonably related to the accompanying chest *x*-ray finding. In the tuberculosis group, however, the arthritis was apparently more severe in general and, in all but one case, had been present for more than 3 years.

TABLE II
CHEST *X*-RAY FINDINGS RELATED TO TYPE OF RHEUMATOID ARTHRITIS

Chest *X*-Ray Findings	Rheumatoid Arthritis		
	Type 1	Types 2 and 3	Total
Normal and Simple Pneumoconiosis	17	12	29
Tuberculosis	11	3	14
Massive Fibrosis and Caplan's	21	11	32
Total	49	26	75

TABLE III
CHEST *X*-RAY FINDINGS RELATED TO DURATION OF RHEUMATOID ARTHRITIS

Chest *X*-Ray Findings	Rheumatoid Arthritis		
	Over 3 yrs	Up to 3 yrs	Total
Normal and Simple Pneumoconiosis	20	9	29
Tuberculosis	13	1	14
Massive Fibrosis and Caplan's	20	12	32
Total	53	22	75

A χ^2-test indicates that these variations between the tuberculosis group and the normal and pneumoconiosis group might have arisen by chance ($P > 0{\cdot}1$ for duration, $P > 0{\cdot}5$ for severity), but in view of the small sample available it is difficult to be certain of this. Moreover, there is some evidence (Cobb and others, 1953; and unpublished personal observations) that infections of all kinds are a notable cause of death in hospital cases of rheumatoid arthritis; and the possibility exists that subjects with severe rheumatoid disease may be prone to tuberculosis. If so, one would expect to find a relatively severe type of arthritis in cases of tuberculosis. Until a larger group of such cases has been examined, it is therefore considered advisable to confine the analysis of the serological results to a comparison of the normal and pneumoconiosis group with the P.M.F. and Caplan group (Table IV).

TABLE IV
CHEST *X*-RAY FINDINGS RELATED TO RESULT OF D.A.T. POSITIVE = RECIPROCAL OF TITRE ≥ 32

Chest *X*-Ray Findings	D.A.T. Result		
	Positive	Negative	Total
Normal and Simple Pneumoconiosis	14	15	29
Massive Fibrosis and Caplan's	28	4	32
Total	42	19	61

Table IV shows that there is a definite correlation between the result of the test and the chest *x*-ray finding, the incidence of positive tests being greater among cases of massive fibrosis. This serological difference between the two groups is equally striking if the actual titres at 18 hrs are compared (Table V, and Figure).

The titres, ranging from $1/<4$ to 1/1,024, are grouped into "low" and "high" responses in Table V.

TABLE V
CHEST *X*-RAY FINDINGS RELATED TO D.A.T. RESPONSE WITH RECIPROCAL OF TITRE ≤ 64 AND ≥ 128

Chest *X*-Ray Findings	D.A.T. Titre Response		
	Low (<4, 4, 8, 16, 32, 64)	High (128, 256, 512, 1,024)	Total
Normal and Simple Pneumoconiosis	21	8	29
Massive Fibrosis and Caplan's	10	22	32
Total	31	30	61

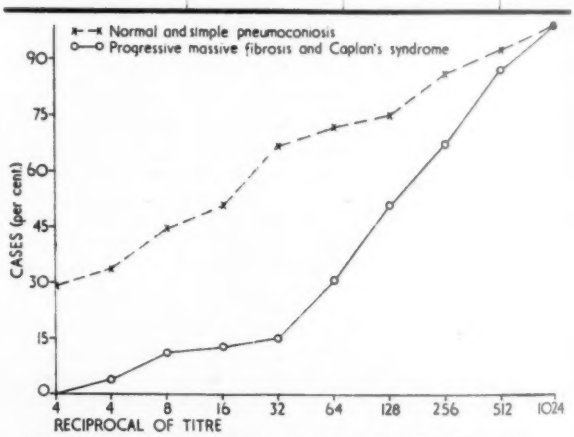

Figure.—Chest *x*-ray findings related to D.A.T. titre response.

Statistical analysis gives for Table IV: $\chi^2 = 9{\cdot}2$ and $P = <0{\cdot}01$; and for Table V: $\chi^2 = 8{\cdot}8$ and $P = <0{\cdot}01$. If a titre of 1/64 is included in the "high" responses, χ^2 becomes 15·8 and $P = <0{\cdot}001$. It may therefore be concluded that, in these cases of rheumatoid arthritis, the appearance of the rheuma-

toid serum factor in relatively high titres is much more likely in the presence of a severe progressive nodular type of pneumoconiosis than in subjects with a normal chest or with simple pneumoconiosis.

Discussion

Although the precise nature and origin of the rheumatoid serum factor (R.S.F.) agglutinating sensitized sheep cells is not known, its occurrence in high titre is probably confined to rheumatoid arthritis and certain closely related syndromes such as disseminated lupus erythematosus (Ball, 1952). Other conditions in which arthritis and constitutional disturbances occur, such as ankylosing spondylitis and rheumatic fever, are negative in the agglutination test. It is also known that the R.S.F. does not reflect variations in the clinical state of rheumatoid arthritis, since the titre may remain high during a natural or therapeutically induced clinical remission. Presumably the R.S.F. is related to a type of tissue response characteristic of rheumatoid arthritis but not closely linked with the constitutional and arthritic manifestations of this disease. Nevertheless, the D.A.T. is most frequently positive in severe classical cases of long duration in which subcutaneous nodules are found.

The present studies show that among subjects with rheumatoid arthritis, both the incidence of positive tests and the titre of the R.S.F. are higher in those with P.M.F. than in those with simple pneumoconiosis or a normal chest *x* ray. Moreover, this difference is not likely to be due to variations in the severity or duration of the rheumatoid arthritis in the various chest disease groups.

The serological results in the P.M.F. group, though not so striking as those of the Caplan group, show the same trend; and it is probable that the presence of massive fibrosis of either type modifies, in some as yet undetermined way, the results obtained with the D.A.T. in subjects with rheumatoid arthritis. Several possible explanations of this finding may be considered:

(1) Subjects whose rheumatoid arthritis is associated with a positive D.A.T. may be more susceptible to P.M.F. than those with a negative D.A.T.

(2) P.M.F. may itself be associated in a proportion of cases with a positive D.A.T. in the absence of arthritis.

(3) The presence of pulmonary tuberculosis which is believed to be an important factor in the pathogenesis of P.M.F. may modify the serological response to rheumatoid arthritis.

At present it is not possible to suggest which, if any, of these possibilities apply. The matter is being further investigated by the serological examination of various non-arthritic control groups, the results of which it is hoped to publish in due course.

Summary

(1) In a sample of rheumatoid arthritis defined by Miall (1955) in an epidemiological study of this disease in a South Wales mining valley, the results of the differential agglutination test were found to vary according to the chest *x*-ray finding.

(2) Both the incidence of positive tests and the titres were higher in subjects with progressive massive pulmonary fibrosis (P.M.F.) than in those with simple pneumoconiosis or a normal chest *x* ray.

(3) This difference was not explained by variations in the severity or duration of the rheumatoid disease in the various chest disease groups.

I am grateful to Professor J. H. Kellgren and to Drs. J. C. Gilson, A. L. Cochrane, and W. E. Miall for their interest and advice.

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Réaction d'agglutination différentielle dans l'arthrite rhumatismale compliquée de pneumoconiose

RÉSUMÉ

(1) Chez un groupe de rhumatisants arthritiques, définis par Miall (1955) au cours de l'étude épidémiologique de cette maladie dans une vallée minière des Galles du Sud, on a trouvé que les résultats de la réaction d'agglutination différentielle variaient selon l'image radiologique de la poitrine.

(2) Aussi bien la fréquence que les titres des résultats positifs étaient plus élevés chez les sujets atteints de fibrose pulmonaire massive et progressive (P.M.F.) que chez les sujets à l'image radiologique normal ou atteints de pneumoconiose simple.

(3) Les variations de la sévérité ou de la durée de la maladie rhumatismale dans les groupes différents de maladie pulmonaire n'expliquent pas cette différence.

Reacción de aglutinación diferencial en la artritis reumatoide complicada de pneumoconiosis

SUMARIO

(1) En un grupo de enfermos con artritis reumatoide, definidos por Miall (1955) en el estudio epidemiológico de esta enfermedad en la cuenca minera de las Gales del Sur, la reacción de aglutinación diferencial varía según el aspecto radiológico del pecho.

(2) Tanto la frecuencia como la intensidad de los resultados positivos fueron mayores en sujetos con fibrosis pulmonar masiva y progresiva (P.M.F.) que en sujetos con pneumoconiosis simple o con radiología pulmonar normal.

(3) Las variaciones de la severidad o de la duración de la enfermedad reumática en los varios grupos de enfermedad pulmonar no explican esta diferencia.

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THE LIVER IN RHEUMATOID ARTHRITIS

BY

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It is generally recognized that rheumatoid arthritis is a systemic disease characterized by profound and widespread disturbances in the connective tissues throughout the body, but having a special predilection for the periarticular and articular structures. Because the supporting framework of parenchymal organs is made up of connective tissue elements, it has been suspected that the function of these organs is altered in patients with rheumatoid arthritis as a result of direct involvement of the supporting framework and/or by secondary morphological alterations of the parenchymatous elements. Thus, the liver has been the subject of investigation by several observers, and its function has been studied to determine whether this organ is involved in patients with rheumatoid arthritis. With the newer techniques of biopsy, liver tissue can be obtained with greater ease, so that the morphologic alterations in the liver may be studied and correlated with liver function tests in patients with various diseases.

The purpose of this report is to present our experience with some laboratory procedures designed to test some of the functions of the liver in one hundred patients with rheumatoid arthritis, and to report the results of examination of liver tissue obtained by needle biopsy in twelve of these patients, and the *post-mortem* findings in the liver of an additional three of these patients.

Review of the Literature

A review of the existing literature relating to the involvement of the liver in rheumatoid arthritis reveals inadequate or contradictory information.

Davis (1936) found a high incidence of increased levels of globulin and decreased levels of albumin in the plasma of patients with rheumatoid arthritis. The blood fibrinogen level was also found to be increased in these patients and there was an inverse relationship between the fibrinogen and globulin levels. Rawls and others (1937) used the azorubin S test as an index of liver function in one hundred patients who had "severe", "moderately severe", or "mild" rheumatoid arthritis: 27 of 34 severe cases (73 per cent.), 21 of 44 moderately severe cases (47·5 per cent.), and seven of 22 mild cases (25·25 per cent.), amounting to 55 per cent. of the entire group, showed liver dysfunction. In addition, these authors also found a slight reduction of the serum proteins and a reversal of the A/G ratio in most of those cases (number not mentioned) that showed liver dysfunction. They found no correlation between the duration of the disease and impairment of liver function, but liver dysfunction was found more frequently in patients who had more severe rheumatoid arthritis.

Rawls and others (1939) reported on the results of several liver function tests in fifty unselected cases of rheumatoid arthritis. The azorubin S test showed some evidence of liver dysfunction in 60 per cent.; the hippuric acid excretion (Quick method) was abnormal in 62 per cent. The bilirubin excretion (Soffer and Paulson method) was abnormal in twelve of 25 cases (48 per cent.); the galactose tolerance test (excretion of 2 g. or more) was abnormal in seven of 25 patients (14 per cent.); the icteric index (index 8 considered normal) was abnormal in 22 cases (44 per cent.); the serum albumin level was abnormal (4 g./100 ml. or less) in 34 cases (68 per cent.); the A/G ratio was abnormal (less than 2) in 38 cases (76 per cent.). The azorubin S test agreed more closely with the clinical evidence of liver damage than any other single test.

Baggenstoss and Rosenberg (1943) reported on the *post-mortem* findings in thirty patients with rheumatoid arthritis whose death was due to various causes. The most frequently observed hepatic lesions were gross atrophy or hypertrophy, chronic passive congestion, fatty changes, "serous hepatitis", and central necrosis. These changes were associated with heart disease and/or inanition. They found no evidence to suggest that the reticulo-endothelial system was stimulated in these patients, nor did they find "any hepatic lesion which could be considered specific".

Perlmann and Kaufman (1946) investigated the serum protein electrophoresis in 23 patients with rheumatoid arthritis. The results suggested an elevation of α globulins during the early course of the disease followed by a predominance in γ globulins in later stages.

Carter and Maclagan (1946) found the serum colloidal gold test to be positive in 76 per cent. and the thymol turbidity test to be positive in 38 per cent. of 34 patients with "atrophic type" of arthritis.

Kalbak (1951) found positive thymol reactions in 75 per cent. of 21 patients with rheumatoid arthritis;

in four, the positive thymol reaction became normal during treatment with cortisone or ACTH. He thought that the positive thymol reaction was due to change in serum proteins.

Archer (1951) found the cephalin flocculation and thymol turbidity tests to be consistently negative in ten patients with rheumatoid arthritis, and in two other patients with both rheumatoid arthritis and degenerative joint disease; the total serum proteins and serum albumin were normal, and the serum globulin tended to be raised. He emphasized that the lowering of the A/G ratio in "non-specific" arthritis was the result of a raised globulin level alone and not of a diminished albumin level.

Schmengler (1952) reported on the findings of liver involvement in thirty cases of "chronic rheumatism"; one of which was examined *post mortem*. The liver was palpable in 21; the Takata reaction was positive in fifteen of the twenty patients; the thymol turbidity test was positive in "most cases". Electrophoretic partition of serum proteins was done in 23: the γ globulin was increased in 70 per cent., the β globulin in 26 per cent., and the α globulin in 35 per cent. Liver tissue was examined in the one autopsied case and in 27 patients obtained by biopsy through the peritoneoscope. In two patients, attempt at biopsy was unsuccessful. All liver specimens were abnormal. Grossly, the liver appeared greyish-red with loss of glistening; the surface was irregular and presented scars, fibrous bands, or reticular arrangement. Microscopically, the cells showed variations in size, fatty degeneration, "reactions of Kupffer cells", haemosiderin accumulations here and there, at times necrosis, perivascular round cell infiltrations, increase in fibrous tissue, and transformation into "rheumatic hepatitis" and cirrhosis.

Movitt and Davis (1953) found no significant abnormalities in the serum albumin level, cephalin flocculation tests, and prothrombin concentrations, or in the morphology of the liver obtained by needle biopsy in seventeen male patients with rheumatoid arthritis, but the incidence of raised serum globulin was high.

The observations relating to the ameliorating influence of liver disease with or without jaundice, pregnancy, and several other diseases upon the manifestations of rheumatoid arthritis are of interest in this connexion. These are adequately discussed by Hench (1940) and will not be repeated here. They led indirectly to the investigations which resulted in the discovery of the beneficial, although temporary, effect of adrenal steroids and ACTH upon the manifestations of rheumatic diseases.

It is readily seen from the foregoing that the results obtained by these investigators have not given us a definite answer to the question whether the liver is involved by the rheumatoid disease process? Our attempts at resolving this problem are hindered mainly by the following difficulties:

(1) Non-hepatic diseases altering the results of so-called liver function tests;

(2) Our inability to distinguish between the effects of systemic disease processes upon the liver and intrinsic liver disease by the available tests of liver function;

(3) The inadequacy of the available histological methods of examination of liver tissue obtained, either by biopsy or *post mortem*, to reveal functional alterations or impairment.

Methods of Study and Procedures

One hundred male patients with rheumatoid arthritis at different stages of severity were observed in the hospital; 77 had involvement of the peripheral joints only, nine had involvement of both peripheral joints and spine, and fourteen had involvement of the spine only. The age of the patients, and duration, stage, and grade of severity of the disease are indicated in Table I.

TABLE I
DISTRIBUTION OF PATIENTS ACCORDING TO AGE, STAGE, SEVERITY, AND DURATION OF DISEASE

Stage of Disease	No. of Patients	Age Group (yrs)	Duration of Disease (range)	Severity of Disease			
				I	II	III	IV
I	20	22–64	6 wks -10 yrs	—	5	10	5
II	30	24–63	3 mths-20 yrs	—	4	13	13
III	22	25–65	8 mths-35 yrs	—	—	14	8
IV	14	28–66	1 yr -35 yrs	—	—	—	14
—	14*	20–55	1 yr -16 yrs	—	—	—	—
Total ..	86+14			—	9	37	60

* Spinal involvement only.

The severity of the disease and resulting functional impairment of the 86 patients who had peripheral joint involvement are graded in accordance with the therapeutic criteria of the American Rheumatism Association (Steinbrocker and others, 1949). The liver function tests, the method of their determination, and the considered normal values are indicated in Table II.

TABLE II
LIVER FUNCTION TESTS

Type of Test	Method	Normal Values
Serum bilirubin	Evelyn and Malloy, 1937	0·2–0·8 mg. per cent.
Serum phosphatase (alkaline)	Bodansky, 1933	2–4 Bodansky units
Bromsulphalein	Rosenthal and White, 1925	Not over 1·6 per cent. in 45 min. (using 5 mg./kg. body-weight)
Total protein, albumin, and globulin	Wolfson, Cohen, Calvary, and Ichiba, 1948	6–8 g./100 ml. (Alb. 3·4–4·5 g./100 ml.; Glob. 2·3–3·6 g./100 ml.)
Cephalin flocculation	Hanger, 1939	Not over 2 per cent. in 48 hrs
Thymol turbidity	Ley, Lewis, and Davidson, 1946	Above 1·4 ml. $BaSO_4$ or above 5 turbidity units
Prothrombin	Quick (one stage), Fisher, 1947	100 per cent.
Total cholesterol	Bloor, Pelkan, and Allen, 1922	150–250 mg. per cent.

Table III shows the patients in whom each type of test was determined, and the patients with peripheral joint involvement are grouped according to the stage of their disease. Twelve patients with involvement of peripheral joints had Vim-Silverman needle biopsies of the liver performed by the transthoracic approach.* In an additional three patients, liver tissue was obtained *post mortem*; two of these patients had severe crippling deformities of the peripheral joints with extensive osteoporosis: one had compression of the spinal cord by collapsed osteoporotic cervical vertebrae and died as a result of pneumonia; the other also died of pneumonia but had, in addition, severe coronary artery disease. The third patient had spinal involvement only and presented the characteristic appearance of "bamboo-spine"; he had severe hypertensive cardiovascular disease and died as a result of rupture of dissecting aneurysm of the arch of the aorta. The pertinent clinical and laboratory data of these fifteen patients are indicated in Table IV.

TABLE III

TYPE AND TOTAL NUMBER OF LIVER FUNCTION TESTS DETERMINED

Type of Test Only	Peripheral Joint Involvement				Spinal Involvement Only	Total Tests
	Stage of Disease					
	I	II	III	IV		
Serum bilirubin	9	22	18	9	13	71
Alkaline phosphatase	7	14	10	11	5	47
Bromsulphalein	9	25	22	12	6	74
Protein	18	27	21	13	12	91
Albumin	18	27	21	13	12	91
Globulin	18	27	21	13	12	91
Cephalin flocculation	10	26	22	12	11	81
Thymol turbidity	11	28	19	12	12	83
Prothrombin	9	27	21	11	7	75
Cholesterol	9	20	15	10	11	65

Results

Table V (overleaf) indicates the type and number of abnormal results grouped by stage of disease. It is readily seen that there is a direct relationship between the severity of the disease, as indicated by the stage of the disease, and the number of abnormal results. Of twenty patients with Stage I rheumatoid arthritis, thirteen (65 per cent.) had

* These biopsies were performed by the members of the Gastro-intestinal Section of the hospital. The liver tissue was fixed in 10 per cent. formalin and stained with haematoxylin and eosin in the usual manner.

SUMMARY OF PERTINENT CLINICAL AND LABORATORY DATA AND MORPHOLOGICAL ALTERATIONS IN OF PAT

Patient No.	Age (yrs)	Severity of Disease	Duration of Disease (yrs)	Erythrocyte Sedimentation Rate (mm./hr) (Wintrobe)	Serum Bilirubin	Alkaline Phosphatase (Bodansky units)	Bromo Sulphalein (per cent.)	Albumin	Glob	halin ulation
1	46	II	6	34	0·5	1·3	Neg.	3·8	3·	eg.
2*	35	II	5/12	36	0·39	3·35	20	3·3	5·	1
3	28	II	6	28	0·48	1·7	Neg.	4·6	1·	1
4	33	II	7	23	0·7	—	Neg.	3·9	3·	2
5	58	II	5	34	0·5	1·8	20	3·5	3·	1
6*	57	II	17	36	—	—	Neg.	3·8	3·	1
7	32	III	8	35	0·5	1·55	Neg.	3·4	4·	2
8	54	III	4	30	0·54	1·2	15	3·6	4·	2
9	44	III	5	32	0·7	—	Neg.	4·2	2·	4
10	55	III	4	35	0·1	—	75	3·1	3·	3
11	44	III	8	37	—	—	Neg.	3·4	3·	2
12	62	IV	21	23	0·5	3·8	Neg.	—	—	3
13*†	58	IV	18	28	0·39	1·2	1·8	2·9	3·4	3
14*†	55	IV	6	36	—	5·1	75	3·6	4·0	3
15†	55	—	26	28	0·8	—	—	3·7	2·6	—

* Liver illustrated in photomicrograph. † Died.

abnormal results. Of thirty patients in Stage II, 26 (86·66 per cent.) had abnormal results. Of 22 patients in Stage III, 21 (95·45 per cent.) had abnormal results. All fourteen patients in Stage IV had abnormal results.

Depression of the serum albumin level was the most frequently found abnormality in Stage I patients. In Stage II patients a raised serum globulin level was the most frequent abnormality (seen in 12), and the serum albumin level was depressed in ten. Similar changes in the albumin and globulin levels were found in Stage III and IV patients.

The cephalin flocculation test was abnormal in five of 26 Stage II patients (19 per cent.). The thymol turbidity test was abnormal in five of 28 Stage II patients (17·8 per cent.). The cephalin flocculation test was abnormal in seven of 22 Stage III patients (31·8 per cent.), and the thymol turbidity in six of nineteen Stage III patients (31·5 per cent.). The cephalin flocculation test was abnormal in six of twelve Stage IV patients (50 per cent.), but thymol turbidity test was abnormal only in one of thirteen Stage IV patients.

The serum cholesterol level was raised in approximately 50 per cent. of Stage I and II patients, but in only three of fifteen patients (20 per cent.) and in only one of ten Stage IV patients.

The serum bilirubin level was normal in all the patients (58 with peripheral joint involvement and thirteen with spinal involvement) in whom it was determined.

The bromosulphalein test was normal in all Stage I patients; it was abnormal in six Stage II patients (24 per cent.), five Stage III patients (22·7 per cent.), and three Stage IV patients (25 per cent.).

Of the fourteen patients who had only spinal involvement, six showed abnormalities in a total of eleven abnormal results, as indicated in Table V.

Microscopic examination of tissue obtained by biopsy in the twelve patients in whom this was performed revealed only minor alterations, chiefly variations in the size and pigmentation of the nuclei of the liver cells, slight prominence of the peripheral fibrous tissue with slight but varying degrees of round cell infiltration, and, occasionally, slight increase of fat. In two of these specimens, these alterations were more pronounced; Figs 1 and 2 (overleaf) depict the most marked of these changes.

In none of these biopsies was the pathologist* able to discern definite evidence of cirrhosis.

* Dr. Joseph M. Young, Pathologist, Veterans Administration Medical Teaching Group (Kennedy) Hospital.

IONS IN OF PATIENTS IN WHOM LIVER TISSUE WAS AVAILABLE FOR EXAMINATION BY BIOPSY OR AT *POST-MORTEM*

Glob	halin ulation	Thymol Turbidity	Prothrombin (per cent.)	Cholesterol (mg. per cent.)	Weight of Liver (g.)	Morphological Changes in Liver	Cause of Death
3·7	eg.	0·6	100	—		Slight prominence of fibrous tissue at portal triads with few round cells Variations in size and pigmentation of nuclei	
5·1	1	2·8	57	340		Moderate increase of fibrous tissue at portal triads with round cell infiltration Fatty metamorphosis	
1·9	1	1·75	100	220		Slight prominence of fibrous tissue at portal triads with few round cells	
3·7	2	1·75	100	215		No significant abnormalities	
3·9	1	3·25	100	—		Fatty metamorphosis	
3·5	1	4·3	45	—		Moderate increase of fibrous tissue at portal triads with round cell infiltration Variations in size and pigmentation of nuclei	
4·5	2	1·0	100	—		No significant abnormalities	
4·6	2	1·75	100	—		Slight prominence of fibrous tissue at portal triads with few round cells Variations in size and pigmentation of nuclei	
2·9	4	0·75	100	187		Slight prominence of fibrous tissue at portal triads with few round cells Variations in size and pigmentation of nuclei	
3·9	3	5·75	100	182		Variations in size and pigmentation of nuclei	
3·7	2	3·5	100	235		Slight prominence of fibrous tissue at portal triads with few round cells Fatty metamorphosis	
—	3	1·75	100	—		Slight prominence of fibrous tissue at portal triads with few round cells	
3·4	3	2·7	100	245	2,250	Slight prominence of fibrous tissue at portal triads with few round cells	Pneumonia
4·0	3	3·5	—	—	1,375	Central zone congestion and infiltration of polymorphs	Pneumonia
2·6	—	—	—	240	1,830	Slight prominence of fibrous tissue at portal triads with few round cells	Aneurysm of aorta

TABLE V

ABNORMAL LIVER FUNCTION RESULTS, SHOWN WITH NUMBER OF PATIENTS TESTED

Type of Test		Peripheral Joint Involvement — Stage of Disease I	II	III	IV	Spinal Involvement Only
Serum bilirubin		0/9	0/22	0/18	0/9	0/13
Alkaline phosphatase		0/7	0/14	1/10	2/11	9/5
Bromsulphalein		0/9	6/25	5/22	3/12	0/6
Total Protein	Depressed	0/18	3/27	0/21	1/13	1/12
	Elevated	0/18	4/27	3/21	1/13	1/12
Albumin	Depressed	4/18	10/27	9/21	9/13	0/12
	Elevated	0/18	2/27	2/21	0/13	1/12
Globulin	Depressed	2/18	2/27	0/21	0/13	1/12
	Elevated	2/18	12/27	12/21	11/13	2/12
Cephalin flocculation		1/10	5/26	7/22	6/12	2/11
Thymol turbidity		0/11	5/28	6/19	1/12	0/12
Prothrombin		2/9	6/27	3/21	3/11	1/7
Cholesterol	Depressed	1/9	1/20	0/15	0/10	0/11
	Elevated	4/9	10/20	3/15	1/10	2/11
Total Abnormal Results		16	66	51	38	11
Total Patients with Abnormal Results	No.	13	26	21	14	6
	%	65	86·6	95·4	100	

The liver obtained at autopsy in the three patients that died likewise failed to show significant morphological abnormalities. One specimen showed congestion and polymorphonuclear infiltration of the central zone areas; this change was thought to be related to the bilateral pneumonic process with small abscesses rather than to the rheumatoid arthritis. Figs 3 and 4 (overleaf) show the microscopic appearance of two of these livers.

Comment

The results suggest that there is a relationship between the severity of rheumatoid arthritis and the hepatic dysfunction indicated by certain liver function tests. Elevation of the serum globulin and depression of the serum albumin were the most frequent abnormalities, closely followed by abnormal cephalin flocculation and thymol turbidity tests. The other tests did not indicate abnormalities in a sufficient number of patients to be of statistical significance. Abnormal liver function tests were found infrequently in patients who had only spinal involvement. Histological examination of the available liver tissue in fifteen of these patients showed only minor alterations. None of the three liver specimens obtained *post mortem* from the three patients who died (disease of Stage IV severity, but inactive, and of 18, 6, and 26 years' duration, respectively) showed any significant abnormalities. Perhaps, however, although haematoxylin-eosin stains did not depict abnormalities, other more refined methods of examination, such as electron microscopy, special staining, and histochemical studies, would have revealed a closer correlation with the liver function tests.

It is difficult to evaluate the significance of these minor morphological alterations. Such changes are seen not infrequently in liver specimens obtained at autopsy from individuals who die of diverse conditions in whom no evidence of liver disease could be found. At the most, these abnormalities could probably be designated by what Popper (1954) termed "non-specific reactive hepatitis". There was no strict correlation between the functions of the liver as appraised by the liver function tests used here and the histological appearance of the liver specimens. Other investigators (Franklin and others, 1948; Popper and others, 1950; Lichtman, 1942) have also commented upon the lack of consistent correlation between the clinical and laboratory findings in liver disease and the histological picture

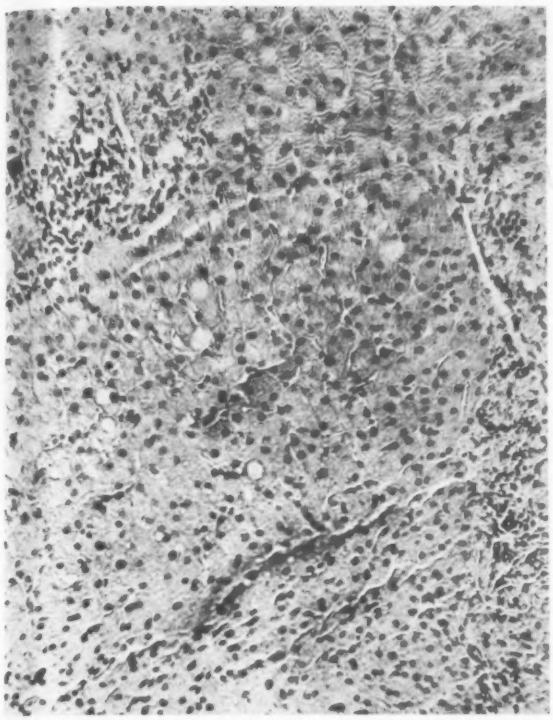

Fig. 1.—Case 2, showing moderate increase of periportal fibrous tissue, round cell infiltration, and slight fatty change.

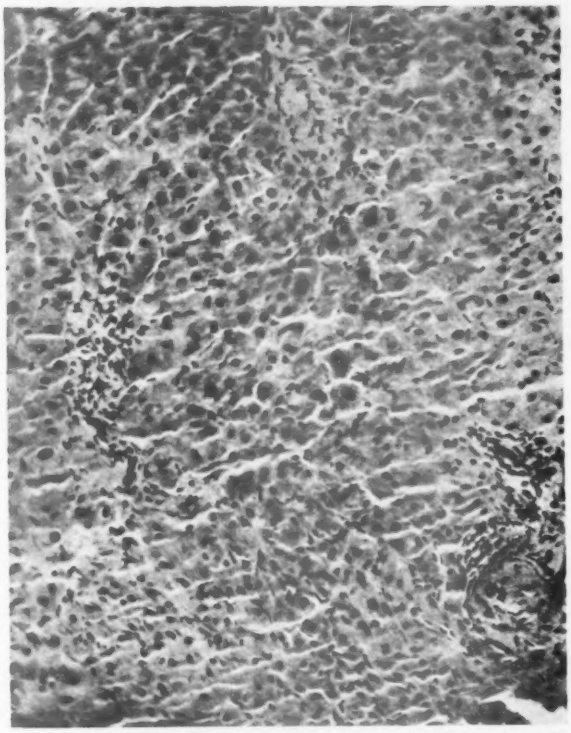

Fig. 2.—Case 6, showing variations in size and staining of nuclei, moderate increase of periportal fibrous tissue, and round cell infiltration.

of liver tissue. Popper (1954) noted that severe hepatic failure was at times associated with relatively few histological alterations, and, conversely, apparently intact liver function was found in patients showing widespread changes in the hepatic parenchyma. These contradictory findings are generally attributed to the fact that the haematoxylin-eosin stained liver sections probably do not depict the functional aberrations of the liver parenchyma. Moreover, the regenerative ability of the liver is so great that impairment of its function can be demonstrated only after extensive liver damage.

The utilization of the so-called liver function tests in assessing the functions of the liver is further complicated by the observation that these tests are non-specific and are not infrequently altered in any chronic disease of whatever aetiology. The abnormal values obtained in these tests could, therefore, be considered to reflect the chronic wasting state so common in rheumatoid arthritics rather than the direct consequence of the rheumatoid process itself. But many observers believe that, although these tests are in a strict sense not liver function tests, they can, nevertheless, be employed to test the functions of the liver. Some of these, notably the protein fractionation, cephalin flocculation, and thymol turbidity tests, reflect a qualitative and probably a quantitative alteration in the serum proteins. Since the liver plays an important role in the elaboration of these proteins, and the serum albumin is thought to be formed only in the liver (Wright, 1952), it can be stated that abnormal values obtained by these tests can be considered to indicate disturbances in liver function. Though our results do not permit an unequivocal answer to the problem "of liver involvement in the rheumatoid process", they appear to justify the opinion that some of the functions of the liver are pathologically altered in patients suffering from rheumatoid disease.

Summary

(1) An attempt has been made to ascertain whether the liver is involved in patients with rheumatoid arthritis.

(2) Liver function tests were performed in 86 patients with rheumatoid arthritis, who had peripheral joint involvement, and in an additional fourteen patients who had only spinal involvement. Of the 86 patients with peripheral joint involvement, nine had spinal involvement also.

(3) Three patients died and liver tissue was obtained for *post-mortem* examination. In twelve

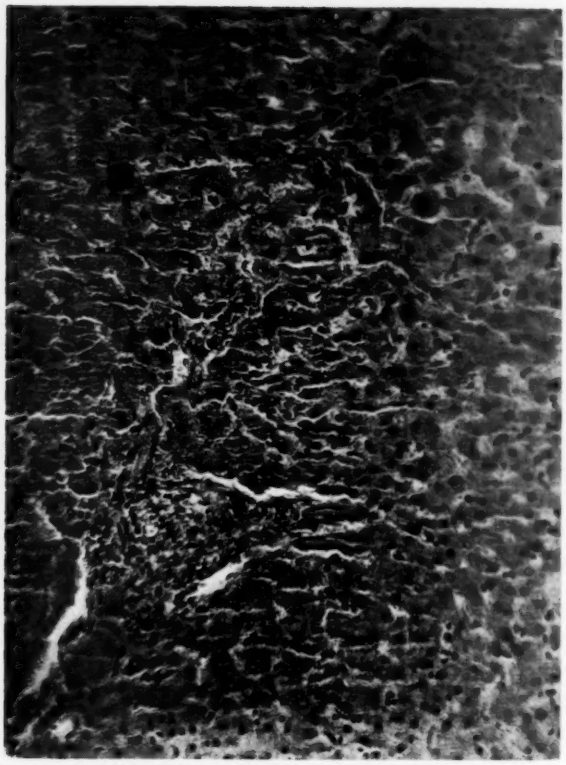

Fig. 3.—Case 13, periportal triad showing slight increase of fibrous tissue and round cell infiltration.

Fig. 4.—Case 14, showing congestion and polymorphonuclear infiltration of central zone area.

other patients liver tissue for examination was obtained by biopsy.

(4) There was a definite relationship between the severity of the disease and the frequency of abnormal results in liver function tests. Elevation of the serum globulin level and depression of the serum albumin level were the most frequently found abnormalities, closely followed by abnormalities in cholesterol, cephalin flocculation, and thymol turbidity.

(5) Histological study of liver tissue revealed definite abnormal morphological alterations only in two out of the fifteen available specimens. These changes are briefly described. The lack of correlation between the clinical and laboratory evidence of liver involvement and the histological appearance of liver tissue is briefly discussed.

(6) Although the results obtained do not allow a definite answer to the problem proposed, the authors believe them to justify the opinion that the functions of the liver are impaired in persons affected by rheumatoid disease.

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Le foie dans l'arthrite rhumatismale

RÉSUMÉ

(1) On a taché de trouver si le foie était impliqué chez les malades atteints d'arthrite rhumatismale.

(2) On fit des tests de la fonction hépatique chez 86 rhumatisants avec atteinte articulaire périphérique et chez 14 autres avec atteinte vertébrale seule. Chez 9 sur les 86 rhumatisants polyarticulaires il y eut une atteinte vertébrale concomitante.

(3) On effectua un prélèvement de tissu hépatique à l'autopsie de 3 malades décédés et chez 12 malades vivants.

(4) On nota un rapport bien déterminé entre la sévérité de la maladie et la fréquence des résultats anormaux des tests de la fonction hépatique. L'augmentation du taux de la globuline sérique et la baisse de celui de l'albumine se virent le plus souvent, suivies de près par des chiffres anormaux du cholesterol, de la réaction de floculation de la céphaline et de la turbidité du thymol.

(5) A l'examen histologique, des altérations morphologiques du tissu hépatique ne furent trouvées que dans deux pièces sur les quinze disponibles. On présente une brève description de ces altérations. On discute sommairement l'absence d'un rapport entre les manifestations cliniques et de laboratoire de l'atteinte du foie et l'apparence histologique du tissu hépatique.

(6) Bien que les résultats obtenus n'offrent pas de solution claire du problème posé, les auteurs croient qu'ils justifient l'opinion que les fonctions du foie seraient altérées dans la maladie rhumatismale.

El higado en la artritis reumatoide

SUMARIO

(1) Se trató de comprobar si el hígado estaba implicado en los enfermos con artritis reumatoide.

(2) Se hicieron valoraciones de la función hepática en 86 enfermos con implicación articular periférica y en 14 con implicación vertebral sola. En 9 de los 86 con implicación periférica la espina participaba del proceso reumático.

(3) Se obtuvo tejido hepático de autopsias al morir 3 enfermos y de biopsias en doce casos.

(4) Se notó una relación determinada entre la severidad de la enfermedad y la frecuencia de los resultados anormales de las determinaciones de la función hepática. Halláronse más frecuentemente cifras altas de globulina sérica y bajas de albumina, seguidas de cerca por valores anormales del colesterol, de la reacción de floculación de la cefalina y de la turbiedad del timol.

(5) Histológicamente, alteraciones morfológicas del tejido hepático encontráronse tan solo en dos preparaciones de las quince obtenidas. Se presenta una breve descripción de estas alteraciones. Se discute brevemente la falta de correlación entre las manifestaciones clínicas y de laboratorio de la implicación del hígado y el aspecto histológico del tejido hepático.

(6) Aunque los resultados obtenidos no ofrecen una solución clara del problema puesto, los autores creen justificada la opinión de que las funciones del hígado están alteradas en la enfermedad reumática.

Ann. rheum. Dis. (1955), **14**, 170.

EFFECTS OF 9-ALPHA-FLUORO HYDROCORTISONE ACETATE ON ADRENAL FUNCTION

BY

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Boland and Headley (1954) described their clinical trials of 9-α-fluoro hydrocortisone acetate (9-α-fF) in the treatment of rheumatoid arthritis. Although salt-retention made the use of this drug in the treatment of rheumatoid arthritis impracticable, they saw in it a new hope, since its existence demonstrated the possibility of producing analogues of hydrocortisone with physiological properties differentially enhanced. The properties studied were the "anti-inflammatory" (anti-rheumatoid in this instance) and the salt retaining. The former was approximately ten times as great as that of hydrocortisone and the latter more like fifty times as great. How does the 9-α-fluoro substitution affect the adrenocortical suppressive action? It would be a great advantage to have a cortisone-like steroid that would supplement the adrenocortical secretion instead of suppressing it and providing a single qualitatively different substitute.

The Figure shows the results of an experiment

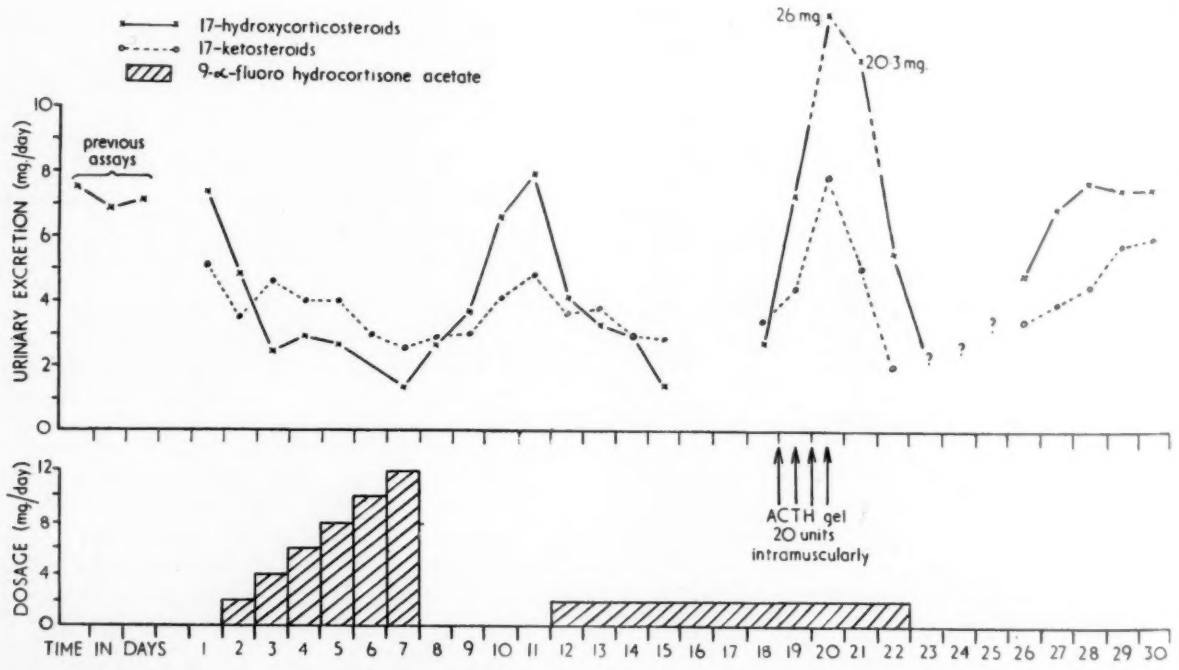

Figure.—Effect of 9-α-fluoro hydrocortisone acetate (given orally to a woman aged 29 with rheumatoid arthritis) on adrenal function measured by daily urinary excretion of 17-hydroxycorticosteroids.

designed to throw light on this question. The patient had early rheumatoid arthritis. She was on a salt-free diet, to minimize fluid retention, during the first period of treatment, but not during the second. The urinary "total 17-hydroxy-corticosteroids (17-OH CS)" assay used was that developed by Dr. J. K. Norymberski at this Centre (Appleby and others, 1954, 1955). The figures recorded on the diagram for 17-OH CS represent the number of mg. excreted daily, less the theoretical recovery, as 17-OH CS, of the administered 9-α-fF (40 per cent.). The patient's control assays show a below average output of 17-OH CS, representing an endogenous secretion of approximately 20 mg. hydrocortisone a day. The results show that as little as 2 mg. 9-α-fF profoundly suppresses the endogenous secretion, suppressing it to the same extent as would ten times as much hydrocortisone. That the suppression was mediated through the inhibition of pituitary ACTH is shown by the excellent response to the administration of ACTH.

Summary

The substitution of a fluorine atom at the 9-α position in the hydrocortisone molecule enhances its ability to suppress adrenocortical function through pituitary ACTH inhibition. The degree of enhancement parallels that of its anti-rheumatic potency.

Thanks are due to Mr. R. D. Stubbs for the chemical assays, and to Dr. Elmer Alpert of Merck and Company Inc. for the 9-α-fluoro hydrocortisone acetate.

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Effet de l'acétate de 9-*a*-fluoro hydrocortisone sur la fonction surrénale

RÉSUMÉ

La substitution d'un atome de fluor en position 9-*a* de la molécule d hydrocortisone renforce sa faculté de supprimer la fonction corticosurrénale par l'inhibition pituitaire de l'ACTH. Son pouvoir antirhumatismal est renforcé au même degré.

Efecto del acetato de 9-*a*-fluoro hidrocortisona sobre la función suprarrenal

SUMARIO

La substitución de un átomo de fluor en posición 9-*a* de la molécula de hidrocortisona acrecenta su poder supresor de la función adrenocortical por inhibición pituitaria de la ACTH. Su poder antirreumático sube paralelamente.

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URINARY EXCRETION OF 17-HYDROXY-20-OXOSTEROIDS IN NORMAL HEALTH AND IN RHEUMATOID ARTHRITIS

BY

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In the course of their outstanding investigations into the urinary excretion of steroids, Dobriner (1951) and Dobriner and others (1951) reported the isolation of 17-α-hydroxypregnanolone (I) from the urine of four out of five patients with rheumatoid arthritis. The daily excretion of this compound (I) recorded for one patient only amounted to 1·5 mg. The authors also reported the absence of (I) from the urine of healthy persons, and its excretion by patients with adrenal hyperplasia and adrenal tumour (Lieberman and Dobriner, 1945; Mason and Strickler, 1947; Miller and Dorfman, 1950), and they concluded that the excretion of (I) in the investigated cases of rheumatoid arthritis pointed to an adrenal dysfunction. More recently Lieberman and others (1954) have detected (I) in a pregnancy urine (0·07 mg./1.), and Dobriner and others (1954) have found it in a case of myelogenous leukaemia (0·5 mg./day), and have noted that small amounts of (I) are found also in normal urine. In view of the latter finding, (I) cannot be considered any longer to be a "pathological" steroid, but its excessive excretion may reflect a derangement of steroid metabolism, as in the adrenogenital syndrome (Jailer, 1954; Appleby and Norymberski, 1955). The information available is insufficient to decide whether rheumatoid arthritis is associated with a metabolic defect manifested by abnormal levels of (I) in the urine. The purpose of the present report is to record some new data bearing on this problem.

(I) contains a molecular fragment which is uncommon among urinary steroids (Figure). This fragment comprises carbon atoms 17, 20, and 21, of which C_{17} is substituted by a hydroxyl group, and C_{20} by an oxo group, and C_{21} is unsubstituted. The class of compounds sharing this structural feature may be termed 17-hydroxy-20-oxosteroids unsubstituted at C_{21}, or 21-deoxy-17 : 20-ketols, or briefly 21-deoxyketols. Appleby and Norymberski (1954, 1955) have recently developed an analytical method for the group determination of such compounds which consists in their selective conversion into 17-oxosteroids (17-ketosteroids) and measurement of the latter by means of the Zimmermann reaction. This method has now been applied to the determination of urinary 21-deoxyketols in normal health and in rheumatoid arthritis.

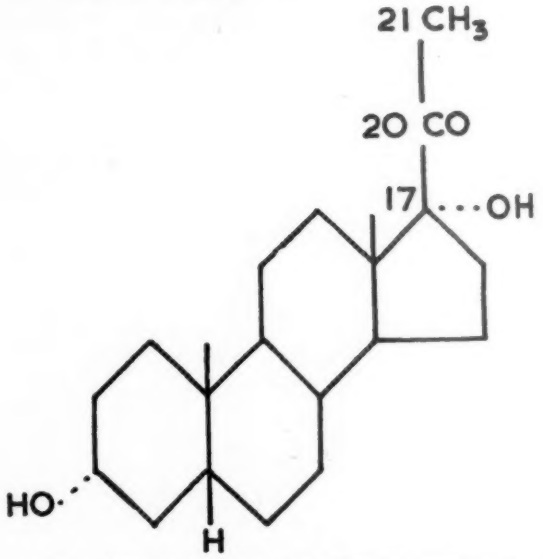

Figure.—Chemical formula of 17-α-hydroxypregnanolone (I).

The investigated group of subjects comprised 26 healthy persons (12 men, 14 women) and 26 patients with rheumatoid arthritis (11 men, 15 women). In one patient the disease was in its early acute phase; in all others the condition was chronic, though of varying duration and severity. Concurrently with the assays of 21-deoxyketols, determinations were performed of 17-ketogenic steroids (17-KGS: Norymberski, 1952; Norymberski and others, 1953;

TABLE

RESULTS OF STEROID ASSAYS

Group	Sex	Subject No.	Age (yrs)	17-KGS* (mg./day)	17-OH CS* (mg./day)	21-deoxyketols* (mg./day)	21-deoxyketols* Mean
Normal Health Average age 36	Women	1	22	12·6	12·6	0·16	0·14
		2	22	11·8	12·3	0·32	
		3	23	17·2	16·1	0·19	
		4	23	5·6	5·7	0·10	
		5	23	10·0	13·7	0·10	
		6	25	14·6	14·0	0·17	
		7	25	16·0	15·9	0·27	
		8	28	6·2	8·1	0·07	
		9	31	8·2	7·8	0·11	
		10	40	12·5	11·9	0·08	
		11	44	—	17·4	0·15	
		12	53	—	13·3	0·03	
		13	62	—	12·4	0·06	
		14	70	—	12·5	0·11	
	Men	15	16	11·0	10·4	0·21	0·26
		16	18	13·1	16·5	0·25	
		17	24	13·0	10·6	0·20	
		18	26	9·6	12·9	0·20	
		19	31	13·8	—	0·40	
		20	35	15·6	17·2	0·46	
		21	37	12·9	13·9	0·25	
		22	43	9·0	9·6	0·20	
		23	46	7·2	6·2	0·34	
		24	51	—	13·7	0·28	
		25	53	13·2	13·2	0·14	
		26	57	—	7·4	0·13	
Rheumatoid Arthritis Average age 51	Women	27	26	7·8	8·4	0·18	0·15
		28	29	—	7·5	0·16	
		29	39	8·0	9·6	0·31	
		30	42	7·2	6·2	0·18	
		31	50	8·4	8·2	0·30	
		32	50	8·6	8·6	0·17	
		33	51	9·4	9·8	0·12	
		34	54	9·6	10·3	0·09	
		35	55	10·4	—	0·10	
		36	55	8·8	10·1	0·11	
		37	57	7·6	8·2	0·10	
		38	63	7·8	8·0	0·08	
		39	63	—	6·3	0·14	
		40	66	11·4	11·7	0·15	
		41	76	7·0	7·4	0·05	
	Men	42	33	—	15·1	0·74	0·32
		43	37	7·4	8·9	0·35	
		44	38	9·6	12·0	0·36	
		45	48	8·8	13·7	0·24	
		46	52	10·6	13·6	0·47	
		47	53	14·6	15·0	0·31	
		48	56	—	9·1	0·32	
		49	56	8·4	11·1	0·19	
		50	58	—	7·2	0·16	
		51	60	11·8	14·3	0·19	
		52	62	—	8·5	0·16	

* Expressed in terms of dehydro*epi*androsterone equivalent to the formed Zimmermann chromogens.

Gibson and Norymberski, 1954) and/or of "total 17-hydroxycorticosteroids" (17-OH CS: Appleby and others, 1954; 1955).

The results of the assays are presented in the Table. The following points merit emphasis:

Within both groups of subjects the daily excretion of 21-deoxyketols was higher in men than in women: normal men excreted 0·13-0·46 mg. (mean 0·26), normal women 0·03-0·32 mg. (mean 0·14); rheumatoid arthritic men excreted 0·16-0·74 mg. (mean 0·32), rheumatoid arthritic women 0·05-0·31 mg. (mean 0·15).

Within each of the four sub-groups there appears to exist a tendency towards lower excretion levels with increasing age. This trend is, however, not so pronounced as to vitiate a comparison between the normal group (average age 36 yrs) and the rheumatoid arthritic group (average age 51 yrs). Only one individual (No. 42) of the latter group had a level of 21-deoxyketols significantly above the normal range; this patient was also the only one whose disease was in its early acute phase. All the other rheumatoid arthritic patients excreted normal amounts of 21-deoxyketols, and the average excretion for the whole group closely approached the normal average.

Though the group of subjects investigated was comparatively small, the results seem definite enough

to allow the conclusion that, in rheumatoid arthritis, or at least in its chronic phase, no grossly abnormal excretion of urinary 21-deoxyketols occurs. The small quantities of urinary 21-deoxyketols found in rheumatoid arthritis circumscribe the excretion levels of 17-α-hydroxypregnanolone (I) and hence the isolation of a comparatively large quantity (1·5 mg./day) of (I) reported by Dobriner and others (1951) in one case of rheumatoid arthritis cannot be considered to represent an abnormality generally associated with the disease.

Discussion

A survey of published relevant data reveals that the average excretion of 17-ketosteroids in rheumatoid arthritis is considerably lower than in normal health (Davison and others, 1947; Desmarais, 1949; Wolfson, 1949; Hench and others, 1950; Devis, 1951; Marti, 1951; Venning and others, 1951; Copeman and others, 1952; Kellie and Wade, 1953; Birke, 1954). Similarly low levels of 17-ketosteroids are, however, found in other chronic diseases (Forbes and others, 1947). Devis (1951) carried out a differential analysis of urinary 17-ketosteroids and observed in ten out of fifteen cases of rheumatoid arthritis a decrease in the percentual content of 11-deoxy-17-ketosteroids. Kellie and Wade (1953) found increased ratios of aetiocholanolone to androsterone in three rheumatoid arthritic patients, but pointed out that Robinson and Goulden (1949) observed a similar trend in cases of prostatic cancer. Birke (1954) found normal excretion patterns of individual 17-ketosteroids in 35 patients with rheumatoid arthritis. The urinary corticosteroid levels reported for the disease are difficult to interpret since different assay techniques were employed (Devis and Lemmens, 1950; Hench and others, 1950; Staub and others, 1950; Conestabile and Volpicelli, 1951; Venning and others, 1951; Copeman and others, 1952). Our own initial figures for 17-ketogenic steroids in rheumatoid arthritis were on the average 40 per cent. below normal values (Norymberski and others, 1953); figures now available for a larger number of patients still show a tendency towards lower values, but the average deviation from normal has decreased to approximately 20 per cent. The blood levels of corticosteroids in rheumatoid arthritis were found to be within normal limits (Nelson and others, 1951).

In our interpretation, the work cited above does not lend support to the view that rheumatoid arthritis is associated with a specific defect in steroid metabolism. Moreover, the detection of 17-α-hydroxypregnanolone (I) in normal urine (Dobriner and others, 1954), together with the evidence here presented, clearly show that, contrary to earlier indications (Dobriner, 1951; Dobriner and others, 1951), an abnormal excretion of (I) has not been demonstrated in rheumatoid arthritis. We wish to emphasize that present knowledge of the steroid excretion pattern in rheumatoid arthritis, or for that matter in any other condition, is only fragmentary, and hence that the conclusions here reached cannot be construed as arguments against a hypothetical causal relation between a derangement of steroid metabolism, or, in particular, between a defect in the adrenocortical function and rheumatoid arthritis.

Summary

The urinary excretion of 17-hydroxy-20-oxosteroids unsubstituted at C_{21} was studied in 26 healthy persons and in 26 rheumatoid arthritic patients. In the analytical test applied, no difference was found between the two groups of subjects. The significance of this finding is discussed in relation to previous reports of an abnormal excretion of 17-α-hydroxypregnanolone in rheumatoid arthritis. It was concluded that the methods so far employed for the study of steroid excretion in rheumatoid arthritis have failed to reveal a specific metabolic defect.

This work was done during the tenure of an Empire Rheumatism Council Research Fellowship by one of us (J.K.N.). We are grateful to Dr. H. F. West for guidance on the clinical aspects of this work and for facilities in his wards. We thank Mr. R. D. Stubbs for assays of 17-ketogenic steroids and of "total 17-hydrocorticosteroids".

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Excrétion urinaire des 17-hydroxy-20-oxostéroïdes normale et dans l'arthrite rhumatismale

RÉSUMÉ

On étudia l'excrétion urinaire des 17-hydroxy-20-oxostéroïdes insubstitués en position C_{21} chez 26 sujets normaux et 26 rhumatisants arthritiques. L'épreuve analytique ne montra pas de différence entre les deux groupes. On discute la signification de ce résultat à la lumière des rapports antérieurs sur l'excrétion anormale de la 17-alpha-hydroxypregnénolone dans l'arthrite rhumatismale. On conclut que les méthodes employées jusqu à présent pour étudier l'excrétion stéroïde dans l'arthrite rhumatismale ont failli de décéler un défaut métabolique spécifique.

Excreción urinaria de 17-hidroxi-20-oxoesteroides normal y en la artritis reumatoide

SUMARIO

Se estudió la excreción urinaria de 17-hidroxi-20-oxoesteroides insubstituidos en posición C_{21} en 26 sujetos normales y en 26 enfermos con artritis reumatoide. Un examen analítico no mostró diferencia entre los dos grupos. Se discute el significado de este resultado a la luz de los relatos anteriores sobre la excreción anormal de la 17-alfa-hidroxipregnenolona en la artritis reumatoide. Se concluye que los métodos empleados hasta ahora para estudiar la excreción esteroide en la artritis reumatoide han faltado de revelar un defecto metabólico específico.

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PARAPLEGIC PARA-ARTICULAR CALCIFICATION

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Abnormal ossification or calcification of the joints is seen in osteo-arthritis, Charcot's joints, and the Pellegrini-Stieda syndrome; less well-known is that seen in the soft tissues not involving the joint surface, consequent upon disease or injury of the nervous system. This condition has a variety of names: "para-osteo-arthropathy" (Dejerine, Ceillier, and Dejerine, 1919); "neurogenic ossifying fibromyopathy" (Soule, 1945); "paraplegic neuro-arthropathy" (Solovay and Solovay, 1949); "para-articular ossification" (Freiburg, 1952).

This condition has been described particularly in paraplegia caused by trauma to the nervous system. Indeed, 40-50 per cent. of patients with traumatic paraplegia have been described by various authors as suffering from abnormal ossification or calcification round the hip or knee joints; these are the joints usually involved, but the condition may occur anywhere below the level of the neurological lesion. However, calcification and ossification do not follow only trauma of the central nervous system. Voss (1937) gives a list of conditions with which they may be associated. This includes lesions not only of the brain and spinal cord, but also of the peripheral nerves.

The present paper describes two cases of para-articular calcification following encephalo-myelitis, and one following craniotomy for a cerebral tumour. In order to form some idea of the incidence, we have examined the radiographs of the hip joints of 51 patients with other nervous diseases causing paraplegia or immobility (Table). Whether ossification or calcification results appears to depend partly on the stage of development (Brailsford, 1941) and partly on the state of the local blood supply (Watson Jones and Roberts, 1934).

TABLE

INCIDENCE OF ABNORMAL CALCIFICATION IN VARIOUS NEUROLOGICAL CONDITIONS

Diagnosis	No. of Cases	No. showing Abnormal Ossification
Paraplegia in the Old	14	—
Disseminated Sclerosis	10	1 (1)
Cerebro-vascular Accidents	6	1
Post-craniotomy, Cerebral Tumour or Abscess	9	—
Spinal Cord Tumour	3	—
Congenital Spasticity	3	— (1)
Post-encephalitis	3	—
Myelitis	2	—
Trauma to Spinal Cord	1	—
Total	51	2 (2)

(Figures in brackets indicate cases with other abnormalities)

Case Reports

Case 1, a male, aged 39, had an attack of measles in April, 1951, followed by encephalo-myelitis. During this time he developed a confusional state, with weakness of the lower limbs; but no details of his neurological condition are available. He remained confused and immobile for 6 weeks, and developed several bed sores. Suprapubic cystotomy had to be performed because of retention of urine. The mental condition improved rapidly after this, and skin grafting over the bed sores was performed in October, 1951.

In December, 1951, the patient was able to get up and walk with help, but developed swelling of the right knee. Although he now had rectal and urinary control, he developed painful frequency of micturition, and cystoscopy showed two large calculi in the bladder.

Examination.—In December, 1951, there was no mental abnormality. There was limitation of all movements of both hips, an effusion into the right knee, with slight limitation of flexion and extension, and limitation of

flexion of the left knee. There were no gross abnormalities in the central nervous system, but both ankle jerks were very brisk, and there was a possible extensor plantar response in the right. Other systems were normal. *X*-ray examination showed calcification round both hips and knees, with calculi in the bladder (Fig. 1).

Serum acid phosphatase	1·2 K.A. units/100 ml. serum
Serum alkaline phosphatase	7 K.A. units/100 ml. serum
Blood urea	36 mg./100 ml. serum
Serum calcium	10·7 mg./100 ml. serum
Plasma inorganic phosphorus	5·2 mg./100 ml. serum

Suprapubic lithotomy (May, 1952) was performed, with relief of the urinary symptoms. Walking improved with re-education, and he was able to walk 2 miles after discharge from hospital. When last seen in June, 1953, he had no symptoms except for his difficulty in walking, and the physical signs remained the same.

The *x*-ray appearance of the hips and knees had not changed.

Case 2, a man, aged 29, began to have double vision, headaches, and numbness of the right arm and leg in July, 1951; 4 months later he was found to have bilateral papilloedema, slight right lower facial weakness, and right-sided spastic hemiparesis, with right extensor plantar response. There was also analgesia to cotton wool and pin prick on the left side, and impaired position sense of the left hand. He was admitted to hospital, and a craniotomy was performed. A mixed glioma was found in the right temporo-parietal region. A portion of the tumour was removed, and deep *x*-ray therapy was given.

The post-operative period was difficult, and the patient was immobile for some time, but made a satisfactory recovery, and was discharged 6 weeks after the operation. There was no evidence of any severe bed sore.

Examination.—On February 4, 1952, he showed only a slight left hemiparesis, without sensory loss. There was, however, limitation of all movements of the hips, right more than left, and limitation of flexion of the left knee. *X*-ray examination showed bony trabeculae between the greater femoral tuberosities and the rims of the acetabulae (Fig. 2, overleaf) and calcification in the medial ligaments of both knees (Fig. 3, overleaf).

Serum calcium	9·5 mg./100 ml. serum
Plasma inorganic phosphorus	4·8 mg./100 ml. serum
Serum alkaline phosphatase	6·5 K.A. units/100 ml. serum

With re-education, walking improved, and the range of joint movement increased, but the *x*-ray appearance remained unchanged. The patient then began to have generalized convulsions; he was re-admitted to hospital on March 3, 1953, with increasing drowsiness, and died 3 weeks later. Permission for necropsy was refused.

Case 3, a man, aged 25, began to complain of headache, with numbness of the legs in 1951. He was admitted to hospital, and was found to have a flaccid paralysis of the left leg, nystagmus, and neck rigidity. He became drowsy, and developed retention of urine, for which a suprapubic cystotomy was performed. His mental condition gradually improved, but he developed incontinence of urine and faeces, with spastic paraplegia. A diagnosis of meningo-encephalitis was made. He was admitted to Black Notley Hospital, where, in spite of physical treatment, he developed flexion contractures of the hips and knees. At this time extensive new bone formation was found about the hip joints.

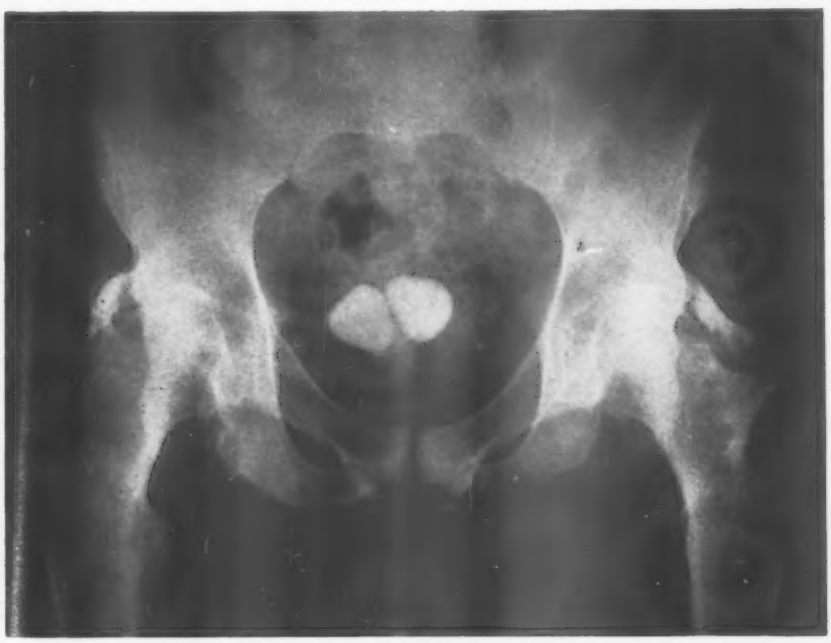

Fig. 1.—Case 1, calcification round hip joints with two calculi in bladder.

Fig. 2.—Case 2, bony trabeculae round both hip joints.

Fig. 3.—Case 2, calcification in medial ligaments of knee joints.

He was discharged after 14 months' treatment, but was re-admitted in April, 1953, when an operation was performed on the right hip. He began to gain control over his bladder and rectum. Otherwise, he was paralysed in the lower limbs, and could move only his left toes.

Examination.—In December, 1953, there was spastic paraplegia, with flexion contracture of the hips and thighs, and analgesia over the lower trunk and thighs. The reflexes of the upper and lower limbs were very brisk. The patient's intelligence was retarded. There were extensive bed sores on both buttocks.

X-ray examination showed extensive new bone formation about both hips, with subluxation of the right hip (Fig. 4). There was also new bone formation around the lower end of the right femur in the quadriceps muscles (Fig. 5).

Fig. 4.—Case 3, bone formation round hip joints with subluxation of right hip.

Fig. 5.—Case 3, bone formation in lower end of right quadriceps muscle, left side normal.

Serum calcium	11	mg./100 ml. serum
Plasma inorganic phosphorus	..	3·1 mg./100 ml. serum
Serum alkaline phostase	.. ..	3·8 K.A. units/100 ml. serum

Metabolic studies performed by Dr. Stuart Mason showed, on urine studies only:

> Negative nitrogen balance (presumably due to immobility), but no abnormality in the calcium or phosphorus. Testosterone inhibited nitrogen drainage as expected, but had no effect on the calcium or phosphorus. Probably this is because the calcium and phosphorus were normal in the first place.

In order to determine the frequency of this condition we reviewed the *x* rays of the hip joints of 51 patients with chronic nervous disorders, who were bed-ridden or immobile. These were mainly paraplegics, but, in view of the findings in Case 2, we included a group of cases who had had a period of a month or more of immobility after craniotomy. The detailed diagnoses are shown in the Table.

Fig. 6.—Linear streak of calcification in region of right hip in a man with disseminated sclerosis.

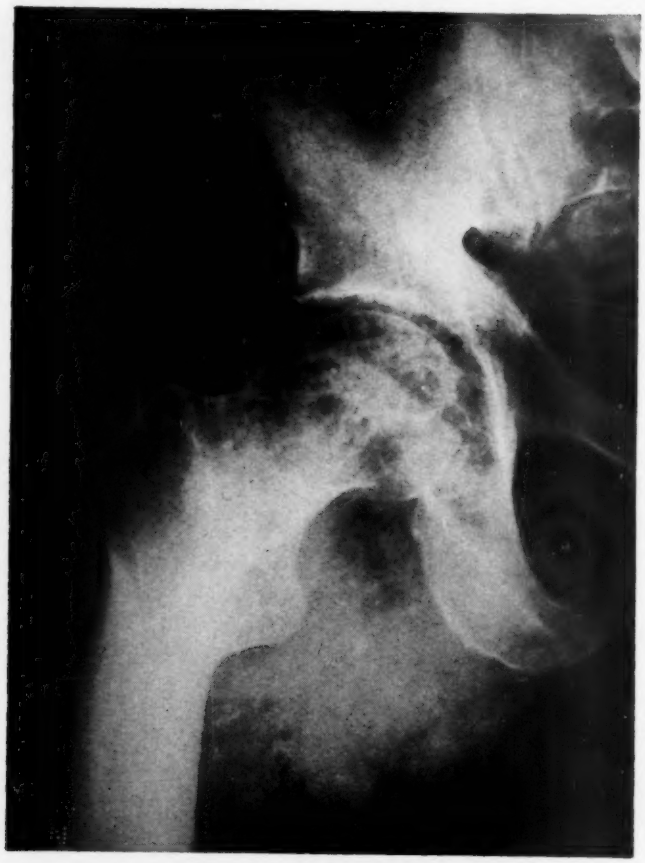

Fig. 7.—Small deposit of calcium near right hip in a man with paraplegia due to cerebro-vascular accidents.

The paraplegias in older people were attributed to arteriosclerosis or to spondylosis. We did not include any cases of Charcot's joints. The incidence of bed sores was often difficult to assess, as many had been bed-ridden for years, and records were not always available for the whole period. However, although small superficial bed sores were common, large deep ones of the type seen in Cases 1 and 2 were found in only four cases, and one of the four had para-articular calcification. Among these 51 radiographs we found only two with an appearance similar to the condition we are describing:

(1) A man, aged 59, had had disseminated sclerosis for many years, with severe spasticity and ataxia. He had been unable to walk for 20 years, had been bed-ridden for 2 years, and had had deep bed sores for 6 months. *X*-ray examination showed linear calcification in the region of the right hip (Fig. 6). The patient died shortly after, and further investigations were not possible.

(2) A man, aged 77, developed a right hemiplegia following a cerebro-vascular accident in April, 1953. He had remained bed-ridden since then, and 4 months later had developed spasticity of the left side, with extensor plantar responses on both sides. An *x* ray taken 9 months later showed small deposits round the right hip (Fig. 7).

Two other cases showed different abnormalities:

(3) A woman, aged 40, with disseminated sclerosis, had a fracture of the pelvis.

(4) A man, aged 35, with congenital spastic paraplegia, had exostoses of the ileum.

These abnormalities appeared to result from spasticity, and not to be comparable with our other cases.

Discussion

Brailsford (1941) and Voss (1937) have described the sequence of events which occur in calcification and ossification of the soft tissues. Changes may be seen as early as 4 weeks after injury. These consist of the deposition of flocculent calcium, which forms into linear streaks, and in the second month undergoes organization, ectopic bone being formed subsequently. In para-articular ossification the ectopic bone formation may involve any of the soft tissues round the hip joint, the capsule, fascial planes, or muscles (Heilbrun and Kuhn, 1947); McNeur (1954), in one *post-mortem* study, found the calcifications mainly on the anterior aspect of the joint. In Case 1 the calcium appeared to lie in the ligaments of the hip joints, whereas in Case 3 the muscles were involved. The medial ligament of the knee joint is sometimes affected, producing an appearance similar to, but more extensive than, the Pellegrini-Stieda syndrome (Case 1). Abramson and Kamberg (1949) and Abel (1950) reported changes in the sacro-iliac joints in some cases, but this was not seen in any of ours.

The high incidence of para-articular ossification in traumatic lesions of the nervous system is well recognized: 49 per cent. (Dejerine, Ceillier, and Dejerine, 1919); 23 out of 62 cases (Soule, 1945); and 43 out of 99 cases (Heilbrun and Kuhn, 1947). Nevertheless, as has been mentioned, many other conditions may be associated. Three cases have been reported recently, after poliomyelitis (Freiburg, 1952), and McNeur (1954) has reported one case after myelitis, with two due to trauma of the spinal cord. It is of interest that Voss (1937) specifically mentions epidemic encephalitis, embolic encephalitis, myelo-encephalitis, and meningomyelitis, all rare lesions. Our Cases 1 and 3 seem to show that conditions of the encephalo-myelitis group are also liable to result in para-articular ossification. Our control group contained only two cases of myelitis, and one of trauma to the cord. The lesions studied in this group were mostly of gradual onset, and this may account for the infrequency with which we found abnormal ossification. Age may be another factor responsible for the absence of ossification, since our 51 patients were mainly elderly.

No satisfactory explanation of para-articular ossification has been found. Many regard the condition as related to Charcot's joints; Solovay and Solovay (1949) reported one case which later developed a condition indistinguishable from a Charcot's joint, and calcification is sometimes seen in the soft tissues surrounding a Charcot's joint of the hypertrophic type. But the two conditions are quite distinct, at least in the early stage. Charcot's joints, although found in a variety of nervous disorders, are mainly seen in tabes dorsalis and syringomyelia, whereas para-articular ossification is mainly seen in paraplegia resulting from trauma and encephalo-myelitis. Also, the factors generally regarded as important in the causation of Charcot's joints—sensory loss and trauma due to weight bearing (Eloesser, 1917)—do not appear to be necessary for the formation of para-articular ossification. Heilbrun and Kuhn (1947) regard pressure on the buttocks from prolonged immobility in bed as a possible traumatic agent, and absence of weight-bearing may account for the preservation of joint surfaces. The aetiological factors responsible for a Charcot's joint have not been fully elucidated, and the trophic function of nerve fibres, although never demonstrated (Delano, 1946), cannot be entirely discounted. Liberson (1953) suggested that a lesion of the sympathetic nerve may be responsible.

A different line of argument suggests that an upset in calcium metabolism may be the cause. In the early stages of immobility there is a negative calcium balance, with mobilization of calcium from the skeleton, sometimes with formation of urinary calculi (Armstrong, 1944) as in Case 1. But para-articular ossification occurs almost exclusively in patients immobilized by nervous disease, and the development of localized myositis ossificans, which Brailsford (1941) believes to be an allied condition, does not depend on immobility alone. We failed to demonstrate any abnormality in calcium balance in Case 3, but the test was performed 2 years after the onset of the condition. Freiburg (1952), because of variation in the serum alkaline phosphatase reading in one case, believed that there might be a transient upset in calcium metabolism, but Soule (1945) found no difference in calcium levels between cases with ossification and otherwise similar cases without, although the plasma organic phosphorus and serum alkaline phosphatase values differed slightly. The calcium, phosphorus, and phosphatase levels were not significantly abnormal in our three cases. A transient renal failure may be a factor, since para-articular calcification was reported in a case of chronic renal failure without paraplegia by Levin and Genovese (1950).

The presence of bed sores has been held to be important. Most cases developing ossification have bed sores, and Heilbrun and Kuhn (1947) and McNeur (1954) believe that the local sepsis may alter the local circulation, and so create conditions suitable for calcification. Soule (1945) found that all his cases with para-articular ossification had bed sores, but that these were also present in many other cases. Three of our cases had severe bed sores, but bed sores were not found about the knees in the patient (Case 1) who showed calcification round the knee joints.

There thus appears to be no satisfactory explanation why one case is affected and another not; Solovay and Solovay (1949) could only suggest that in some patients an individual diathesis might predispose them to the development of ossification.

Summary

Three cases of para-articular calcification or ossification are described: two of encephalomyelitis, and one of cerebral neoplasm with craniotomy.

In a series of 51 patients with chronic nervous disorders, only two had slight calcification round the hip joints. Patients with paraplegia due to trauma of the central nervous system and encephalomyelitis appear to be particularly liable to develop this complication, which develops mainly in younger people.

The aetiology of the condition is discussed. No satisfactory explanation has yet been found.

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Calcification paraplégique para-articulaire

Résumé

On décrit trois cas de calcification ou ossification para-articulaire: deux d'encéphalo-myélite et une de néoplasme cérébral avec craniotomie.

Dans une série de 51 malades manifestant des troubles nerveux chroniques, seulement deux d'entre eux présentaient une légère calcification autour de l'articulation de la hanche. Les malades ayant une paraplégie consécutive à un traumatisme du système nerveux central et à l'encéphalo-myélite semblent être particulièrement susceptibles de souffrir cette complication qui attaque surtout des personnes plutôt jeunes.

On discute l'étiologie de cette affection qui n'a pas encore d'explication satisfaisante.

Calcificación paraplégica para-articular

Sumario

Se describen tres casos de calcificación o de osificación para-articular: dos de encefalomielitis y un de neoplasma cerebral con craniotomia.

En una serie de 51 enfermos con disturbios nerviosos crónicos, sólo dos manifestaron una ligera calcificación alrededor de la articulación coxo-femoral. Enfermos con paraplegia consecutiva a un traumatismo del sistema nervioso central y a la encefalomielitis parecen particularmente susceptibles a esta complicación, que ataca generalmente personas jóvenes.

Se discute la etiología de esta afección, que todavía no tiene explicación satisfactoria.

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LIVER FUNCTION IN RELATION TO POSSIBLE ABNORMALITIES OF STEROID METABOLISM IN RHEUMATOID ARTHRITIS

BY

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Sommerville, Marrian, Duthie, and Sinclair (1950) claimed to have shown conclusively that in patients suffering from rheumatoid arthritis an abnormally high proportion of progesterone administered by the intramuscular route was excreted in the urine as pregnanediol. Further results pointing to the same conclusion were subsequently obtained by Sommerville (1950).

These findings were thought to be of possible significance in connexion with the aetiology of rheumatoid arthritis, since the symptoms of that disease were known to be suppressed by cortisone, which is closely related chemically to progesterone and may be metabolized in the body in much the same way. As a preliminary to more extensive investigations which were being planned, it was thought desirable in the first instance to extend the observations on progesterone metabolism in a further series of normal and rheumatoid arthritic subjects.

Before the completion of this further series it was clear that, contrary to the findings of Sommerville and others (1950) and Sommerville (1950), there was no marked abnormality in the pregnanediol excretion in the majority of rheumatoid arthritic subjects, but, since some of the latter showed pregnanediol recoveries outside the range which had been regarded as "normal" by Sommerville and others (1950), it was felt that further investigations would be advisable.

There is some evidence from studies on human subjects and experimental animals that severe liver dysfunction may be associated with an abnormally high urinary excretion of pregnanediol after the administration of progesterone (Paschkis, Cantarrow, and Havens, 1951; Russell, 1952). Furthermore, it has been claimed by some authors (Rawls, Weiss, and Collins, 1939; Hench, Bauer, Dawson, Hall, Holbrook, Key, and McEwan, 1941; Miller, 1935; Darby, 1953) that abnormalities in liver function occur not infrequently in rheumatoid arthritic subjects. Accordingly the possibility was considered that the apparent abnormalities in progesterone metabolism observed in some rheumatoid arthritic subjects might be confined to those with abnormalities in liver function. In view of this possibility, and of the conflicting results reported by various authors, it was decided to undertake a thorough investigation of liver function by a number of recognized tests in an unselected group of patients suffering from rheumatoid arthritis. This part of the study was specifically designed to investigate the possible association of impairment of liver function with abnormal progesterone metabolism. Only those cases showing significant abnormalities in liver function were to be submitted to tests of progesterone metabolism. At the same time it was decided to extend the observations on progesterone metabolism in a further group of normal and rheumatoid subjects.

The two parts of the investigation were to a large extent carried out independently. The results of the work on liver function are presented in Part I of this communication and those on progesterone metabolism in Part II.

I. Liver Function in Rheumatoid Arthritis

During the past 30 years many conflicting reports have appeared on liver function in relation to rheumatoid arthritis. The metabolism in the liver of protein and of carbohydrate has received most attention, but, although there is general agreement on the existence of abnormalities in protein metabolism, no such agreement can be found with respect

of carbohydrates. The more general functions of liver—regulation of enzyme activity, detoxification, bile pigment and cholesterol metabolism, and secretory and excretory functions—have been much less widely investigated.

Hench and others (1941), in a general review of clinical and biochemical findings in rheumatoid arthritis, summarized previous work. They concluded that there is no evidence of any gross liver dysfunction, but stressed the difficulty of devising liver function tests delicate or specific enough for use in conditions where a minor dysfunction is suspected. The method of plasma protein fractionation used by early workers has been supplanted by the newer electrophoretic techniques. In this way, Routh and Paul (1950) were able to follow the plasma protein pattern throughout the different phases of the disease, and to show a direct relationship between the degree of abnormality and the severity of the disease. Other workers have confirmed these results. Despite this marked abnormality in protein metabolism, there is evidence of only slight quantitative and qualitative differences in the amino-acid composition of blood or urine (Borden, Wallraff, Brodie, Holbrook, Hill, Stephens, Kent, and Kemmerer, 1950). Creatine levels in both blood and urine are reported as normal by Dawson and Salt (1952).

The hippuric acid recovery test, in which administered benzoic acid is conjugated with glycine in the liver, has been used to study detoxification. Lemon, Chasen, and Looney (1952), using this test in a study of glycine metabolism (20 per cent. of the amino-acid residue in collagen consists of glycine), found normal recovery figures in all stages of rheumatoid arthritis, except in severe cases when wasting was present, and in these blood glycine levels were reduced. From these results they concluded that the liver is functioning normally in arthritis, low recoveries being due to extrahepatic demands on glycine reserves. Rawls and others (1939), on the other hand, reported a high percentage of abnormal hippuric acid recovery values in patients suffering from rheumatoid arthritis.

These authors also claimed that 60 per cent. of their patients gave a high recovery figure in the azorubin S test, suggesting a dysfunction of the liver's secretory and excretory function. No abnormal results were found by either Robinson (1943) or Lemon and others (1952), using the bromsulphophthalein test. The methods used by Rawls and Lemon are open to criticism in that slight alteration in either bile or blood volume will markedly affect the results.

The liver would appear to be functioning normally in rheumatoid arthritis as judged by the activity of plasma alkaline phosphatase (Steinberg and Suter, 1939), and of cholinesterase (Grob, Lilienthal, Harvey, and Jones, 1947). There are, however, very few figures available, and little significance can be placed on isolated values as they give no indication of the general trend of the enzyme activity of the individual.

Block, Buchanan, and Freyberg (1941) and Lemon and others (1952) found no abnormality in either cholesterol or phospholipid metabolism in rheumatoid arthritis. During wasting and malnutrition, Wells, Lowrey, and Ross (1951) found low plasma cholesterol levels, but normal levels are reported in less severe stages of the disease.

Knowledge of the metabolism of bile pigment is scanty, the figures for plasma bilirubin being varied and unreliable (Rawls and others, 1939). Pemberton and Foster (1920) were the first to report evidence of abnormal carbohydrate metabolism in rheumatoid arthritis. In a group of sixty patients, a high proportion showed decreased glucose tolerance following the oral administration of 100 g. glucose. They stated that there was a definite relationship between the degree of abnormality and the activity of the arthritis. Improvement in the disease was accompanied by a return to a more normal response. Shackle and Copeman (1933) confirmed the finding of Pemberton and Foster, but Kersley (1937) reported that sugar tolerance was normal in the majority of cases. Flynn and Irish (1946) used Soskin's intravenous glucose tolerance test to eliminate possible errors arising from faulty absorption from the alimentary tract. They compared rates of clearance in 64 cases of rheumatoid arthritis and sixty normal controls; in only 12·5 per cent. of the rheumatoid group had the blood sugar level returned to normal within 60 minutes as compared with 71·7 per cent. of the controls. To investigate the possibility that the delayed clearance in rheumatoid arthritis might be due to diminution of peripheral glycogen depots in the presence of muscle atrophy, they applied the test to nineteen cases of severe poliomyelitis. The curves in all these patients showed a more rapid clearance than in healthy controls.

The results of fructose tolerance tests performed by Kimball (1932) and by Miller (1935) are contradictory, but may be disregarded as both authors measured total blood sugar and so lost the advantages of this test. Although glucose tolerance tests gave normal results in all of eleven cases studied by Weber (1939), Wells and others (1951) found evidence of slight abnormality. Rawls and others (1939) reported an abnormality in the metabolism

of galactose in 14 per cent. of patients examined, but did not stress these results as they considered the test unsatisfactory.

Methods and Materials

The tests were chosen to cover as wide a range of liver function as possible, and, with few exceptions, the methods used were the standard procedures described in the literature:

The following tests were performed:

(1) Plasma bilirubin (Haslewood and King, 1937)
(2) Urinary urobilinogen (Wallace and Diamond, 1925).
(3) Bromsulphophthalein retention test (Ingelfinger, Bradley, Mendeloff, and Kramer, 1948).
(4) Hippuric acid test (Quick, 1940).
(5) Serum alkaline phosphatase (Bessey, Lowry, and Brock, 1946).
(6) Serum cholinesterase (Michel, 1949).
(7) Plasma cholesterol (Kerr and Bauld, 1953).
(8) Zinc turbidity (Kunkel, 1947)
(9) Thymol turbidity (Shank and Hoagland, 1946).
(10) Plasma protein pattern (Tiselius' electrophoretic technique, Tiselius, 1938).
(11) Urinary amino acid composition (Dent, 1951).
(12) Fructose tolerance test (Stewart, Scarborough, and Davidson, 1947).

Initially the tests were performed, where possible, on a group of students, and the figures so obtained were found to fall within the normal range given by the authors of the methods. In all, 44 hospital patients were examined; 29 of these suffered from rheumatoid arthritis, the remaining fifteen being patients from a general medical ward. This latter control group was considered more suitable for comparison with the rheumatic group in respect to age, general mobility, and diet than healthy young students.

The 29 patients with rheumatoid arthritis represented a random sample of the admissions to the Rheumatic Unit, Northern General Hospital. All presented unequivocal signs of the disease and were admitted because of the need for hospital treatment. Patients in the control group had been admitted to hospital for a variety of conditions, but in the majority (thirteen of fifteen) the blood sedimentation rate was within the normal range at the time of the investigation. A note was made of the diagnosis and clinical history in each case. The distribution in the rheumatoid group with regard to sex, age, duration of disease, clinical assessment, haemoglobin level, and erythrocyte sedimentation rate is shown in Table I.

Basic information regarding the controls is also shown, but details of diagnosis and duration of disease are omitted as no significant correlations were apparent.

A low fat, high carbohydrate diet was given for 4 days before and throughout the three days of the test period. All drugs were withheld. Urine was collected for the first 24 hours. The various tests were performed during the next 2 days. Fasting blood was used for all determinations and the time of withdrawal controlled in order to avoid any diurnal variation.

One patient, with cardiovascular disease and an enlarged liver in addition to rheumatoid arthritis, gave abnormal results in nearly every test on two occasions, and these have been omitted from the general discussion.

TABLE I

AGE, SEX, AND CLINICAL ASSESSMENT OF RHEUMATOID PATIENTS AND CONTROLS

Subjects		Rheumatoid Arthritis	Controls
Sex	Male	9	9
	Female	20	6
Age (yrs)	15–40	5	9
	41–60	19	1
	61+	5	5
Duration of Disease (yrs)	0– 2	12	—
	3– 9	10	—
	10+	7	—
Clinical Assessment	Severe	12	—
	Moderate	17	—
Erythrocyte Sedimentation Rate (mm./hr)*	0–29	10	13
	30–59	9	2
	60+	10	0
Hb per cent. 14·8 g. = 100 per cent.	40–69	9	0
	70–79	10	1
	80+	10	14

* E.S.R. was measured in Westergren tubes, using blood treated with Wintrobe's dry mixture of ammonium and potassium oxalate as anticoagulant.

Results

Plasma Bilirubin and Urobilinogen.—No evidence of abnormality in the metabolism of bile pigment was found in any of the cases examined. Values for bilirubin were all well below the level of 1·2 mg. per cent. Urobilinogen was present in amounts too small to be detected in dilutions exceeding 1 : 20, with the exception of one case in which a positive result was obtained at a dilution of 1 : 30.

Hippuric Acid Recovery Test.—Using the conditions laid down by Quick (1940), 45-55 per cent. of benzoic acid fed to normal individuals can be recovered as hippuric acid in the urine. The results in 25 of 28 cases of rheumatoid arthritis fell within this range. In three patients recoveries were below 45 per cent. (40, 43, and 28); the last result might be explained by an incomplete urine sample, the volume being very low. Among the fifteen controls only one low recovery (40 per cent.) was recorded.

Serum Alkaline Phosphatase.—In only one rheumatoid patient did alkaline phosphatase activity exceed the normal range. It was subsequently shown that this patient also suffered from Paget's disease.

In the control groups results all fell within the normal range.

Serum Cholinesterase.—Results in both controls and rheumatoid patients fell within the normal range of 0·6 to 1·2 units.

Plasma Cholesterol.—Using a chromatographic method, no abnormality was found in either the total cholesterol level or the ester-free ratio in any case studied.

Urinary Amino Acids.—Although the results of separating urinary amino acids by paper chromatography cannot be interpreted on a strictly quantitative basis, they give a reasonably good general picture. Compared with results in controls and normal individuals there was no evidence of a quantitative or qualitative difference in the pattern of amino acids excreted by patients suffering from rheumatoid arthritis. Glycine, glutamic or aspartic acid, serine, lysine, valine, and occasionally taurine were present.

Zinc and Thymol Turbidity Tests.—When the results of these tests were expressed as standard units (Table II) no values outside the normal range were recorded in the group of healthy students. In the control group of hospital patients abnormal values were found in a small number (Z.T., 1; T.T., 5). In the 28 rheumatoid patients there was a much higher proportion of abnormal results (Z.T., 8; T.T., 19).

TABLE II

DISTRIBUTION OF TURBIDITY FIGURES*

Groups	Zinc Turbidity			Thymol Turbidity		
	Normal Range		16–24	Normal Range		12–20
	0–8	8–16		0–4	4–12	
Students	7	3	0	8	0	0
Rheumatoid Patients ..	10	10	8	9	15	4
Controls	9	5	1	10	5	0

* Figures expressed as standard units.

Plasma Protein Pattern.—In the early stages of the investigation the plasma protein pattern was examined in twelve patients by the moving boundary Tiselius electrophoresis technique. A 2- to 3-fold increase in fibrinogen was found in every case. The A/G ratio was reduced, and in those showing the most abnormal patterns there was a slight decrease in the α- and β-globulin fractions.

In Fig. 1 (opposite), the electrophoretic pattern of the plasma proteins from a normal individual (*a*) is contrasted with those from three rheumatoid patients; (*b*) represents the typical pattern in rheumatoid arthritis; (*c*) reveals the presence of an exceptionally large amount of γ-globulin, and (*d*) a very high fibrinogen content. These observations are in accordance with those reported by other workers.

Fructose Tolerance.—It is known that a significant proportion of glucose is metabolized outside the liver. In order to obtain more accurate information as to carbohydrate metabolism within the liver, the fructose tolerance test was used in the present investigation. It is agreed that the liver is largely responsible for the metabolism of this sugar. The method of estimation is specific for fructose which is not normally present in the peripheral blood. Results may therefore be considered more reliable than those obtained when glucose is used. Stewart and others (1947) claim that, in normal subjects after the ingestion of 50 g. fructose, the level of fructose in the blood never exceeds 20 mg. per cent. and falls to below 8 mg. per cent. in 2 hours. The distribution of results in the rheumatoid and control groups (hospital patients) are shown in Table III.

TABLE III

DISTRIBUTION OF FRUCTOSE TOLERANCE TEST FIGURES

Groups	Maximum			2-hr Value		
	Normal Range		20–25	Normal Range		8–12
	10–15	15–20		0–4	4–5	
Rheumatoid Patients ..	6	13	7	0	13	13
Controls	6	6	1	0	11	2

Among 26 rheumatoid patients, the results were abnormal in sixteen (60 per cent.), seven (23 per cent.) exceeded the maximum limit of 20 mg. per cent., and thirteen (50 per cent.) showed values above 8 mg. per cent. at the end of 2 hours. Only one (8 per cent.) of the thirteen controls exceeded 20 mg. per cent., and two (16 per cent.) showed slight delay in clearing the sugar from the blood.

Bromsulphophthalein Test.—The percentage disappearance rate of the dye from the blood after intravenous injection of 150 mg. bromsulphophthalein/sq. m. body surface was measured in 27 patients. In this method results are independent of blood volume, and, within reasonable limits, of the dose. Samples of blood (0·2 ml.) were obtained by finger prick, 6, 12, 18, 24, and 30 min. after injection. The cells were spun out after dilution to 1 ml. with 0·9 per cent. NaCl. 0·8 ml. of the supernatant was transferred to a second tube containing 0·2 ml. 0·5 N NaOH, and the colour thus developed was compared with that of a sample of blood

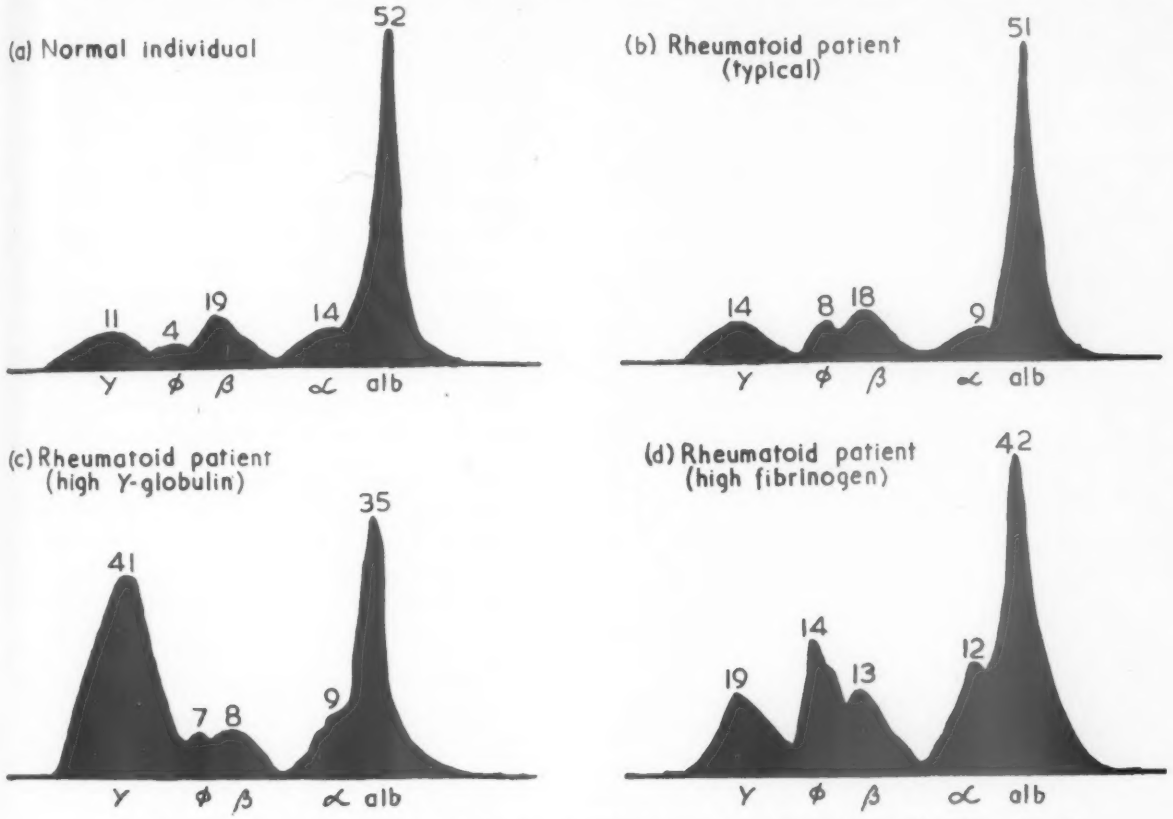

Fig. 1.—Electrophoretic pattern of plasma proteins in a normal individual (*a*), and three rheumatoid patients (*b*, *c*, *d*). Each protein fraction is given as a percentage of the total protein.

obtained before injection of the dye. The results were plotted on a semi-logarithmic scale and the percentage disappearance rate per minute calculated. No difference was found between the values obtained in the rheumatoid group and from five healthy controls. Both sets of results were within the range of 12-14 per cent. The mean value given by Inglefinger and others (1948) for normal individuals is 13·8 per cent. Darby (1953), using the method of Mateer and others (1943) reported that in a group of fifty rheumatoid patients, 23 per cent. showed a significant degree of retention of bromsulphophthalein when the results of the tests were compared with those obtained in a control group of 45 hospital patients. In view of his findings, it was decided to re-examine, by the method of Mateer and others (1943), eleven of the original patients who were still available. The test was also applied in sixteen additional cases of rheumatoid arthritis and fifteen patients in an orthopaedic ward. The results are presented in Table IV (overleaf).

Using this method no dye should remain in the blood 45 min. after injection. It will be seen that the mean value for dye retained at 45 min. in the 27 rheumatoid patients (0·5 per cent.) does not significantly exceed that limit. The control group as a whole does not show a significant retention (1·7 per cent.), but two individuals retained 8·5 per cent. and 4·5 per cent. of the dye at 45 min., though no history of liver disease was obtained in either of them. Taking all values below 1 per cent. as representing clearance, 10 per cent. of the rheumatoid patients and 50 per cent. of the control group were over this value at 45 minutes. At 30 min. the corresponding values in the two groups were 77 and 80 per cent. It is obvious that these results do not agree with those reported by Darby (1953). Although there is no significant retention of dye in either group, the control group tends to show a higher retention than the rheumatoid group. A histogram of the retention figures is given in Fig. 2 (overleaf).

Discussion

No comment is necessary except on the positive findings in the turbidity tests and protein fractions, the dye retention, and the fructose tolerance test.

TABLE IV

PERCENTAGE RETENTION VALUES OF BROMSULPHOPHTHALEIN

Controls			Rheumatoid Patients		
Case No.	Percentage Retention		Case No.	Percentage Retention	
	30 min.	45 min.		30 min.	45 min.
1	5·4	2·0	1	2·7	0·0
2	—	2·0	2	2·4	0·9
3	2·2	1·0	3	4·9	0·9
4	2·9	0·0	4	5·1	0·6
5	3·2	1·6	5	1·4	0·0
6	0·0	0·0	6	6·1	1·0
7	0·0	0·0	7	2·0	0·0
8	2·5	0·0	8	1·8	0·0
9	5·0	2·9	9	1·6	0·0
10	2·0	0·9	10	4·3	2·0
11	11·0	8·5	11	3·7	0·0
12	1·1	0·0	12	5·1	1·0
13	5·2	2·2	13	2·0	0·0
14	0·0	0·0	14	2·3	0·5
15	9·0	4·5	15	2·5	0·6
			16	1·0	0·0
			17	1·0	0·2
			18	1·5	0·2
			19	1·4	0·2
			20	5·1	1·3
			21	0·5	0·0
			22	5·5	2·7
			23	1·3	0·0
			24	0·9	0·0
			25	0·7	0·2
			26	4·6	0·5
			27	0·0	0·0
Mean ±S.D.	3·2±2·7	1·7		2·6±1·7	0·5

The exact significance of the zinc and thymol turbidity tests in relationship to protein metabolism in the liver is not clear. Martin (1949) thought that abnormal thymol turbidities associated with liver damage depend on a disturbance of the intimate relationships of the serum albumin and globulins. Qualitative defects in albumin appear to be important in the production of the reaction in acute hepatitis, but abnormal globulins which contribute to the reaction have been demonstrated in the sera of patients with no other evidence of liver disease. The intensity of the turbidity also depends on the amount of lipid in the serum (Maclagan, 1944; Kunkel and Hoagland, 1947). Reactions above the normal range in the zinc turbidity test are associated with alterations in the globulins. A much higher incidence of positive reactions occurred with thymol than with zinc in the group of rheumatoid patients.

The number of positive reactions in the control group of hospital patients was very much less. A study of the plasma protein pattern in rheumatoid patients revealed abnormalities of varying degree, but the A/G ratio was reduced in the majority. An increase in γ-globulin and a slight reduction in α- and β-globulins were found in those with the most abnormal patterns. Positive turbidity tests would be expected in these circumstances, but there is no direct evidence that these changes in the plasma protein pattern in rheumatoid arthritis can be related to hepatic dysfunction. Similar deviations from the normal pattern occur in a wide variety of diseases in which other evidence of liver damage is absent. No satisfactory explanation for the marked increase in fibrinogen commonly found in the active phase of rheumatoid arthritis has ever been offered, but this abnormality is not a feature in cases with other evidence of liver damage. There is no satisfactory proof of a hyperimmune reaction in rheumatoid disease, but this possibility must be considered in seeking an explanation for alterations in the globulin fractions.

Investigation of carbohydrate metabolism by the fructose tolerance test revealed a significant difference between rheumatoid patients and controls, but the delay in clearing the sugar from the blood in the former was not very marked. This evidence of slight impairment of carbohydrate metabolism in the liver is in agreement with results reported by a number of other workers.

Using the method of Ingelfinger and others (1948) for the bromsulphophthalein test, the percentage disappearance rate in all rheumatoid patients fell within the normal range. No significant retention of

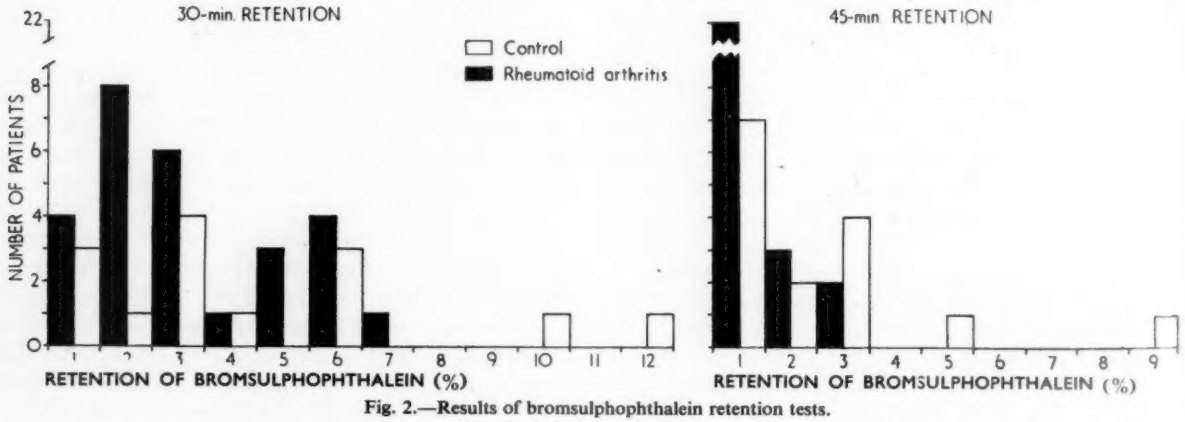

Fig. 2.—Results of bromsulphophthalein retention tests.

dye was demonstrated in rheumatoids or controls when the method of Mateer and others (1943) was used. The results reported by Darby (1953) were not confirmed.

These results indicate that there is minimal evidence of liver damage in patients suffering from rheumatoid arthritis, but it is possible that the tests here reported are not sufficiently sensitive to reveal functional abnormalities which may be of significance in the pathogenesis of this disease.

II. Urinary Excretion of Pregnanediol after Administration of Progesterone in Normal Individuals and Patients with Rheumatoid Arthritis

Methods.—Experimental subjects were injected intramuscularly with 50 mg. progesterone dissolved in 50 ml. olive oil, and 24-hour urine specimens were collected from each subject on the day before the injection and on the following 4 to 5 days. Pregnanediol determinations in duplicate were carried out on each specimen by the method of Sommerville, Gough, and Marrian (1948), and the total pregnanediol excretion calculated after correction for the "urine blank". Experiments were carried out on seventeen rheumatoid arthritic men, nine rheumatoid arthritic women, eight normal men and one normal woman.

Results.—These are shown in Fig. 3A, the results obtained by Sommerville and others (1950) and Sommerville (1950) being recorded alongside for the sake of comparison (Fig. 3B).

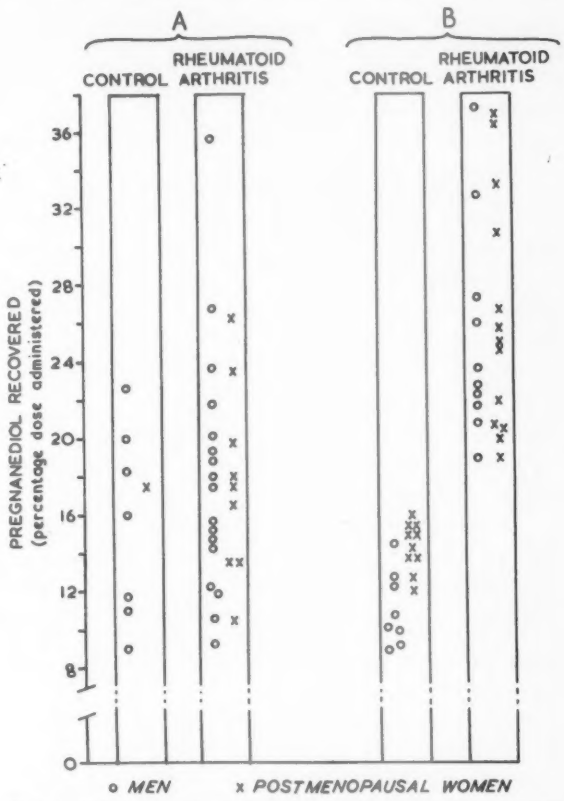

Fig. 3.—Urinary excretion of pregnanediol by normal and rheumatoid arthritic subjects after intramuscular progesterone.
(A) Present investigation, using a single dose of 50 mg. progesterone.
(B) Sommerville and others (1950) and Sommerville (1950), using two doses of 60 mg. progesterone on successive days, or a single dose of 60 mg. progesterone.

Discussion.—Although in the present work experiments were carried out on nine normal subjects only, it is clear that the normal range of pregnanediol recovery is considerably wider than was suggested by Sommerville and others (1950) and Sommerville (1950). In fact, four of these nine subjects showed pregnanediol recoveries which previously would have been regarded as abnormally high.

Of the 26 rheumatoid arthritic cases studied, 21 showed pregnanediol recoveries within the normal range as determined in the present work, and no fewer than eleven showed recoveries falling within the normal range of Sommerville and others (1950) and Sommerville (1950).

It is clear that, contrary to the claim of Sommerville and others (1950), there is no consistent difference between normal and rheumatoid arthritic subjects in the urinary excretion of pregnanediol after the intramuscular administration of progesterone. No satisfactory explanation of the discrepancy between the present findings and those of Sommerville and others (1950) and Sommerville (1950) can be put forward.

Since it has now become apparent that the metabolism of administered progesterone as judged by urinary pregnanediol excretion is not significantly abnormal, and since no satisfactory evidence of impairment of liver function had been obtained in the majority of patients investigated, the concept that there might be some association between the abnormal metabolism of progesterone and impaired liver function in rheumatoid arthritis has had to be abandoned.

Summary

(1) The results of a number of routine tests of liver function in patients with rheumatoid arthritis have been compared with those in other patients.

(2) There was no evidence of abnormality in the metabolism of bile pigment, excretion, detoxification, or enzyme activity in the liver in either group.

(3) In rheumatoid patients the plasma protein pattern was abnormal in a number of respects.

There was a marked increase in fibrinogen, a reduction of the A/G ratio, a decrease in the α- and β-globulins, and an increase in the γ-globulin. The zinc and thymol turbidity tests were positive in the majority of cases. There was no significant change in the pattern of amino acids in the urine. It is not considered that these signs of disturbance in protein metabolism necessarily arise as a result of altered liver function.

(4) Mild impairment of carbohydrate metabolism in the liver is suggested by delay in the clearance of fructose from the blood.

(5) Earlier reports of abnormal metabolism of progesterone have not been confirmed.

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La fonction hépatique par rapport à des anomalies probables du métabolisme des stéroides dans l'arthrite rhumatismale

RÉSUMÉ

(1) On a comparé les résultats d'un certain nombre de tests systématiques de la fonction hépatique chez des malades atteints d'arthrite rhumatismale avec ceux obtenus chez d'autres malades.

(2) On n'a pas trouvé d'anomalies concernant le métabolisme du pigment biliaire, l'excrétion, l'activité antitoxique ou enzymatique dans le foie de deux groupes.

(3) Chez les rhumatisants on a trouvé des anomalies des protéines plasmatiques revêtissant plusieurs aspects: le fibrinogène était bien augmenté, le rapport albumine/globuline diminué, les fractions alpha et beta de la globuline diminuées et la fraction gamma augmentée. Dans la plupart des cas les tests de turbidité du zinc et du thymol étaient positifs. On n'a pas observé de changement appréciable dans le tableau des acides aminés dans l'urine. On ne croit pas que ces signes de dérangement du métabolisme des protéines dérivent nécessairement de l'altération de la fonction hépatique.

(4) Le temps prolongé de l'élimination sanguine de la fructose suggère l'existence d un dérangement bénin du métabolisme carbohydré.

(5) On n'a pas confirmé les rapports antérieurs selon lesquels le métabolisme de la progestérone serait altéré.

La función hepatica en relación a las anomalías probables del metabolismo de los esteroides en la artritis reumatoide

SUMARIO

(1) Se compararon los resultados de un número de determinaciones sistemáticas de la función hepática en enfermos con artritis reumatoide con los obtenidos en otros enfermos.

(2) No se encontraron anomalías del metabolismo del pigmento biliar, excreción, actividad antitóxica o enzimática en el hígado de ambos grupos.

(3) En los reumáticos varios aspectos del cuadro de las proteinas plasmáticas viéronse alterados: el fibrinogeno fué apreciablemente aumentado, el cociente albumina/globulina disminuído, las fracciones alfa y beta de la globulina disminuídas y la fracción gama aumentada. En la mayoría de los casos las reacciónes de turbiedad del zinc y del timol fueron positivas. No se vío cambio apreciable en el cuadro de los amino-ácidos en la orina. No se cree que estas manifestaciones de desarreglo del metabolismo de las proteinas sean necesariamente el resultado de la alteración de la función hepática.

(4) La prolongación de la eliminación sanguínea de la fructosa sugiere la existencia de un desarreglo benigno del metabolismo carbohídrico.

(5) No se confirmaron los relatos anteriores según los cuales el metabolismo de la progesterona sería alterado.

Ann. rheum. Dis. (1955), **14**, 191.

COLD PRECIPITABLE HAEMAGGLUTINATING FACTOR IN SERUM FROM PATIENTS WITH RHEUMATOID ARTHRITIS

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The agglutination test with sensitized sheep erythrocytes, first described by Meyer (1922) and rediscovered by Waaler (1940), and by Rose and others (1948), has attracted increasing interest. Since 1948 the present authors have been making various types of investigations into the test in question (Svartz, 1952). The correlation between the haem-agglutinating serum factor and rheumatoid arthritis is extremely interesting in view of our observations that this factor is a component present in almost all specimens of blood sera from patients suffering from this disease. Joint fluid from patients suffering from rheumatoid arthritis gave the same results as serum (Svartz and Schlossmann, 1950). Cortisone and ACTH have no—or only a very slight—influence on the test (Svartz, 1950) (Table I).

It was shown with ever-increasing clarity that not infrequently the reaction turned out to be positive in other diseases besides rheumatoid arthritis (Svartz and Schlossmann, 1952). Next to rheumatoid arthritis, lupus erythematosus disseminatus is the disease that has given the largest number of positive reactions. In addition, other "collagen diseases" (such as scleroderma, dermatomyositis, and peri-arteritis nodosa) give with relative frequency a positive haemagglutination test. The test is usually negative in ankylosing spondylitis, and the same is true of rheumatic fever, but here a slightly positive test is sometimes recorded. Septic arthritis and tuberculous arthritis showed negative results in our series.

From the theoretical as well as from the practical point of view, it is important to keep in mind that the reaction is occasionally positive in disorders other than collagen diseases, such as diseases of the liver, and myeloma.

Manifestly, therefore, it was highly desirable to try to make the reaction more specific in regard to rheumatoid arthritis. Since earlier observations had shown that the haemagglutinating factor accompanies the globulin fraction, it seemed important to find out whether different types of fractionation of serum proteins could throw a clearer light on the degree of specificity of the reaction. The Cohn

TABLE I

HAEMAGGLUTINATION TEST ON SERUM FROM RHEUMATOID ARTHRITIS BEFORE AND AFTER TREATMENT WITH CORTISONE IN A MALE PATIENT

Date	Stage of Treatment	Dilution													Titre
		1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1,024	1:2,048	1:4,096	1:8,192		
29.3.50	Before treatment with Cortone	4	4	3	3	2	2	2	1	1	1	1	0	0	4,096
6.4.50	Before treatment	3	3	3	3	2	2	2	2	2	1	1	1	0	8,192
11.4.50	Immediately before treatment	3	3	3	2	2	2	2	2	1	1	1	0	0	4,096
18.4.50	During treatment	4	4	3	3	2	2	1	1	1	1	1	1	0	8,192
24.4.50	During treatment	3	3	3	3	3	2	2	2	1	1	1	1	0	8,192
26.4.50	During treatment	4	4	3	3	3	3	2	2	1	1	1	1	0	8,192
29.4.50	3 days after treatment	4	4	3	3	3	3	3	2	1	1	1	1	0	8,192
8.5.50	12 days after treatment ..	4	4	3	3	2	2	2	2	1	1	1	1	0	8,192

fractionation gave no results of any significance, and the same was the case with several other fractionating methods. It was not until the method of fractionating with CO_2 was tried that any interesting results were obtained (Svartz and Schlossmann, 1953a, c). It was found by this method that there are at least three types of haemagglutinating factors. The factor that induces haemagglutination in lupus erythematosus, for instance, is not identical with the haemagglutinating factor in rheumatoid arthritis. Nevertheless, the different groups could not be clearly distinguished from one another by the CO_2 method.

The method that has yielded the best results so far is fractionation by *precipitation in cold.* The blood serum from a patient suffering from rheumatoid arthritis, having first been inactivated and freed from heterophil agglutinins, is mixed with distilled water in the proportion 1 : 14 and allowed to stand in +4° C. for 48 hrs. A precipitate is then produced (Svartz and Schlossmann, 1953b, c). The same also applies to many other sera, but the extremely interesting circumstance could be observed that the cold precipitable fraction from rheumatoid arthritis is practically the only one that contains the haemagglutinating factor in question. In lupus erythematosus the haemagglutinating factor is left in the supernatant fluid and cannot be shown to exist in the precipitate (Table II).

TABLE II

HAEMAGGLUTINATION TEST PERFORMED WITH REDISSOLVED COLD PRECIPITATE FROM SERUM

Clinical Diagnosis	Haemagglutinating Factor in Cold Precipitate	Haemagglutinating Factor in Supernatant Fluid
Rheumatoid arthritis ..	+	(+)
Other collagen diseases .. (lupus erythematosus disseminatus, scleroderma, dermatomyositis)	0	+

Our investigations show that there is in sera from patients with rheumatoid arthritis a substance that is, practically speaking, specific for that disease. It is a well-known fact that no biological reaction is absolutely specific for one disease only, but in regard to the reaction with the rheumatoid factor the exceptions are strikingly few. Thus, only in rare cases of other diseases, could an insignificant quantity of haemagglutinating factor be demonstrated in the cold precipitable fraction of serum. We are justified, then, in speaking of a specific rheumatoid arthritis test, giving positive results in 90-95 per cent. of cases of the disease. It should be noted, however, that the test does not become positive until after the first 2 months of the disease.

We have sought to analyse the cold precipitate further by means of electrophoresis.

Different fractions of the cold precipitate have been obtained with Carlson's modification of zone-electrophoresis (Carlson, 1954). For purposes of comparison the electrophoretic diagram from serum before treatment in cold is shown first. The number of fractions examined is 25 (Fig. 1, opposite).

As was to be expected from earlier investigations, the haemagglutinating factor was bound to the gamma-globulin fractions. Experiments were now conducted with redissolved cold precipitate from the same serum as in the foregoing diagram (Fig. 2, opposite).

In proportion to the serum the sample is concentrated eight times. A high peak was obtained in the γ-globulin, starting on the borderline between β- and γ-globulin. The fractions corresponding to the peak in the diagram showed a clear and distinct haemagglutination reaction.

Certain observations indicate that the factor giving rise to the haemagglutination is not a normally existing γ-globulin. These investigations on the substance in question are not yet completed.

Svartz (1951) reported on some investigations on the inhibition of the haemagglutination. It was found that an inhibitor could be experimentally induced in rabbits by injecting into them serum or joint fluid from patients suffering from rheumatoid arthritis. Sera from rabbits injected with serum from blood-donors showed only a slight increase in the anti-haemagglutinating effect. During the past year studies have been made on the inhibitor of the haemagglutination induced in rabbits by injections of the cold precipitable factor. The capacity for inhibition could be increased to about 1 in 1,000 by injecting the redissolved cold precipitable haemagglutinating factor intravenously, showing that this factor can act as an antigen. In addition, it was demonstrated that sera from normal rabbits were capable of inhibiting the haemagglutination up to a dilution of 1 : 64. The fact that normal rabbit serum sometimes has a rather pronounced capacity for inhibition must be considered when using a rabbit amboceptor serum for the haemagglutination test. It is necessary to use an amboceptor serum with high haemolytic titre, *viz.* 1 in 4,000-6,000, so that the quantity of amboceptor serum used for the haemagglutination tests must not be high. It is interesting to note that normal human serum and horse serum absorbed with normal sheep cells did not exhibit any anti-haemagglutinating capacity. For these tests, 0·5 ml. human serum, resp. horse

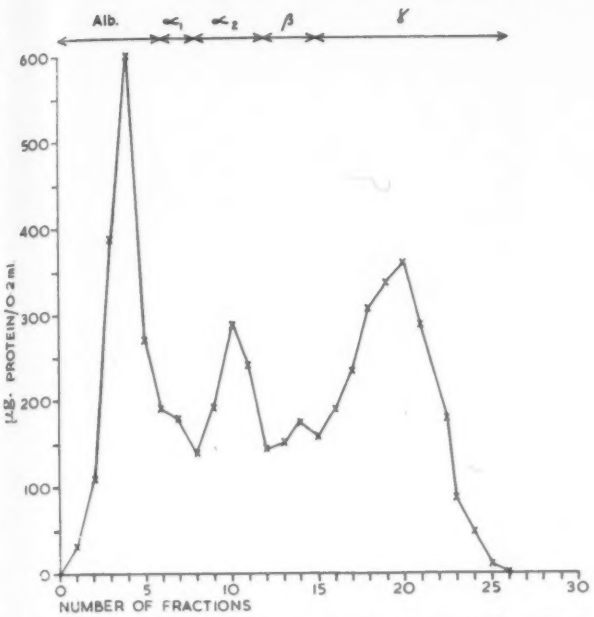

Fig. 1.—Zone electrophoresis on serum from rheumatoid arthritis. (Method of L. Carlsson.)

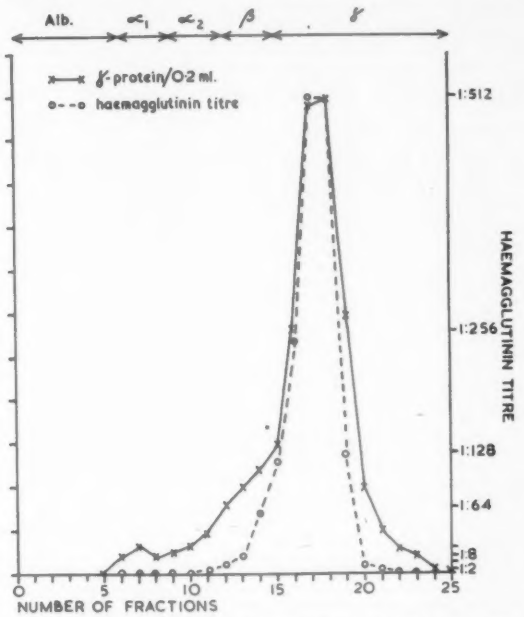

Fig. 2.—Zone electrophoresis on redissolved cold precipitate from the same rheumatoid arthritis serum as in Fig. 1, but concentrated eight times. Haemagglutination test made with the various fractions obtained by zone electrophoresis.

serum, and 0·5 ml. serum from patients suffering from rheumatoid arthritis were mixed, placed in a water bath at 37° C. for 60 min., and then tested for sheep-cell agglutination.

Another question of theoretical interest is which parts of the erythrocytes react with the amboceptor and the haemagglutinating factor. It seemed probable that the haemoglobin was of no importance in this respect. Large amounts of erythrocytes were haemolysed and the stroma washed with saline solution. The reaction performed with this stroma treated with amboceptor showed an agglutination.

Experiments have also been made to discover some method of creating experimentally the factor characteristic of rheumatoid arthritis. We shall here touch upon only one of these series.

Certain types of non-haemolytic cocci, the classification of which is not yet clear, were cultivated from the throats of patients with rheumatoid arthritis. Collagen tissue (from tendons and peri-articular tissue) was used as the culture medium. The bacteria having been allowed to grow for some time on the substratum, they and other particles in the culture were removed by centrifugation. As from serum, cold precipitate was obtained from the culture fluid. The redissolved cold precipitable substance showed a haemagglutination reaction of the same type as precipitate from rheumatoid arthritis serum (Table III).

Our observations show that the haemagglutinating factor is induced by enzymes, which are formed by the bacteria. It is obvious that several types of bacteria have the capacity to form the enzyme here in question, but in this connexion it is interesting to note that haemolytic streptococci and staphylococci have not shown the phenomenon in question.

Our investigations seem to indicate that the specific haemagglutinating factor in rheumatoid arthritis is induced by enzymatic influence upon the collagen tissue in the organism.

TABLE III

HAEMAGGLUTINATION PRODUCED BY REDISSOLVED COLD PRECIPITATE FROM BACTERIA-FREE FILTRATES OBTAINED FROM CULTURES OF NON-HAEMOLYTIC COCCI

Strain of Bacteria	Haemagglutination Titre								
	1 : 4	1 : 8	1 : 16	1 : 32	1 : 64	1 : 128	1 : 256	1 : 512	1 : 1,024
R–dt	3	2	2	2	1	1	1	1	0
L–n	2	2	2	2	2	1	0	0	0

Summary

A substance characteristic of rheumatoid arthritis exists in the blood and synovial fluid of patients with that disease. This substance is able to agglutinate sensitized sheep erythrocytes.

This haemagglutinating factor can be demonstrated in cold precipitate from blood serum, but only in exceptional cases do cold precipitates from sera other than rheumatoid arthritis give rise to a slight haemagglutination.

The haemagglutinating factor is found in the γ-globulin fraction of serum, but apparently it is neither a pure γ-globulin nor a normal one.

Rabbit serum, but not normal human serum or horse serum, usually contains a factor inhibiting the haemagglutinating reaction.

The stroma of erythrocytes and not the haemoglobin reacts with the amboceptor in sensitization.

A haemagglutinating factor with the same properties as the serum of rheumatoid arthritis can be created experimentally by culturing certain types of bacteria (non-haemolytic cocci) on collagen tissue. In these experiments the haemagglutinating factor could be recovered from the bacteria-free culture fluid. The results indicate that enzymes produced by the bacteria give rise to the haemagglutinating substance through their effect on the collagen tissue.

To judge from the investigations so far carried out, it is probable that the specific haemagglutinating substance in serum taken from patients with rheumatoid arthritis is formed as a result of enzymatic influence upon the collagen tissue in the organism.

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Le facteur hémagglutinant dans le sérum chez les malades atteints de la polyarthrite chronique évolutive

Résumé

Dans la polyarthrite chronique évolutive (arthrite rhumatoide) se trouve, dans le sang et dans le liquide synovial, une substance qui est caractéristique pour cette maladie. Cette substance a la faculté d'agglutiner les globules rouges sensibilisés du mouton.

Le facteur hémagglutinant s'attache à la fraction de globuline γ du sérum, mais il ne s'agit ni d'un γ-globuline normal ni d'un globuline pur.

Le sérum des lapins contient généralement un facteur qui empêche la réaction de l'hémagglutination. Le sérum de l'homme ou celui du cheval ne contiennent pas ce facteur.

C'est le stroma des globules rouges et non l'hémoglobine qui réagit avec l'ambocepteur dans la sensibilisation.

Expérimentalement, on peut provoquer un facteur hémagglutinant possédant les mêmes propriétés que le facteur du sérum dans l'arthrite chronique évolutive. Cela s'est montré possible, entre autres, en cultivant certaines bactéries sur le tissu conjonctif. Le facteur hémagglutinant, pouvait dans ces essais, être constaté dans le liquide de culture dégagé de bactéries. Le résultat de ces expériences montre que c'est des enzymes produites par les bactéries qui provoquent le facteur hémagglutinant, par son action sur le tissu conjonctif.

A en juger par les recherches déjà faites, il est vraisemblable que la substance spécifique hémagglutinante du sérum chez les malades atteints d'arthrite chronique évolutive, est formée par l'action des enzymes sur le tissu conjonctif de l'organisme.

El factor hemoaglutinante en el suero de enfermos con artritis reumática

Resumen

En el artritis reumática crónica hay en la sangre y en el líquido sinovial una substancia que es característica de esta enfermedad. Tiene el poder esta substancia de aglutinar los hematíes sensibilizados de oveja.

Pertenece el factor hemoaglutinante a la fracción de γ-globulina del suero, pero no es ni una γ-globulina pura ni una γ-globulina regular.

En el suero del conejo hay generalmente un factor que puede impedir la reacción de hemoaglutinación. En el suero del hombre o del caballo no existe este factor. Es el estroma y no la hemoglobina de los glóbulos rojos que reacciona con el amboceptor en la sensibilización.

Se puede producir experimentalmente un factor hemoaglutinante con las mismas propiedades que el factor de suero de artritis reumática crónica. Se ha podido hacer por ejemplo por cultivar ciertas bacterias en tejido colageno. En estos experimentos se ha demostrado el factor hemoaglutinante en el líquido de cultivo descargado de bacterias. Muestran estas investigaciones que son fermentos producidos por las bacterias que produce el factor hemoaglutinante por su influencia sobre el tejido conjunctivo.

Según las investigaciones que se han hecho hasta ahora parece probable que se forma la substancia hemoaglutinante específica en el suero de enfermos con artritis reumática crónica por influencia de fermentos sobre el tejido conjunctivo del organismo.

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SERUM ANTIPLASMIN AND PLASMIN IN RHEUMATOID ARTHRITIS

BY

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The antitryptic activity of rheumatoid serum has been investigated by a number of workers (Coke, 1949; Ragan and others, 1949). Coke has shown that the extent and activity of the disease, in 200 cases of rheumatoid arthritis, was accompanied by an increase in the antitryptic function of serum.

Todd (1949), using streptokinase-activated plasminogen, found a decrease in proteolytic activity during the acute phase of rheumatic fever. The present paper is concerned with alterations in the levels of streptokinase-activated serum plasminogen and serum antiplasmin in rheumatoid arthritis. The serum antiplasmin-plasmin (streptokinase-activated) system was chosen rather than the spontaneous fibrinolytic action of plasma, as the latter has a low degree of activity (Macfarlane and Biggs, 1946; Biggs, Macfarlane, and Pilling, 1947), is labile (Fearnley, Revill, and Tweed, 1952; Truelove, 1953; Fearnley and Tweed, 1953), and is not inhibited by normal plasma (Bidwell, 1953).

Methods

(1) *Measurement of Plasmin Activity.*—Patients' sera were obtained with sterile precautions, cooled immediately to 4° C., and used as soon as possible. The precursor was obtained from the serum by the method of Milstone (1941), 0·5 ml. aliquots of serum being used. This was activated with 0·2 ml. streptokinase (equivalent to 200 Christensen units), and incubated for 15 min. at 37° C.

The proteolytic activity was estimated by a slight modification of the method of Remmert and Cohen (1949), a barbitone-HCl buffer (*p*H 8) being used in preference to a phosphate buffer, since this gave greater *p*H stability. The optimum substrate concentration of 4 per cent. casein found by Rennert was confirmed. Under these conditions the *p*H optimum curve gave a sharp peak at *p*H 8. A linear relationship was obtained between the enzyme concentration and the acid soluble "Tyrosine" released (Fig. 1—limits 50-200 μg. "Tyrosine" per hour).

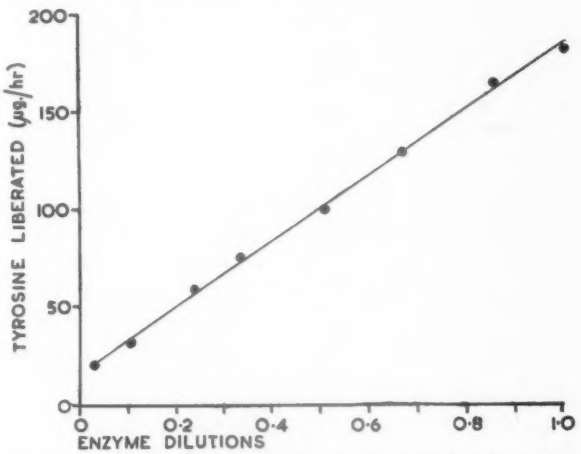

Fig. 1.—Relationship between enzyme concentration and μg. acid-soluble "tyrosine" liberated per hour.

(2) *Measurement of Antiplasmin.*—Plasma, obtained from the blood bank, was used to prepare plasminogen by the method of Milstone (1941). The precursor was prepared in bulk (usually from 2-l. quantities of plasma), dialysed for 24 hrs against distilled water at 4° C. freeze dried, and stored at −15° C.

On each day that antiplasmin estimations were performed, a sample of the precursor was removed, activated with streptokinase, and diluted with barbitone-HCl buffer (*p*H 8), to give an activity corresponding to a release of 200 μg. acid soluble "Tyrosine" per hour at 37° C. The diluted, streptokinase-activated enzyme, henceforth referred to as the standard enzyme, was used for the measurement of antiplasmin. This was done by adding 0·2 ml. of the patient's serum to 0·5 ml. standard enzyme and incubating at 37° C. for 30 min. Estimation of the residual activity was performed as above, and the

results were expressed as a percentage of the standard enzyme activity (100 per cent. = 200 μg. acid soluble "Tyrosine" per hour at 37° C.). A linear relationship was obtained between the serum concentration and the percentage activity (Fig. 2—limits 10-100 per cent. activity).

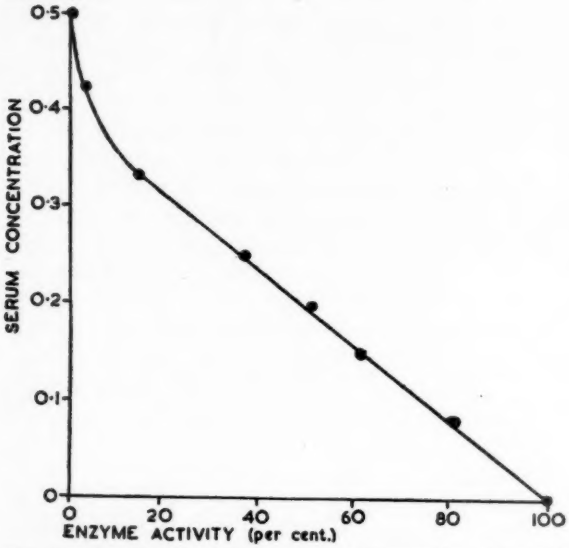

Fig. 2.—Relationship between serum concentration and activity expressed as percentage of a standard enzyme preparation.

Results

The controls were healthy, ambulant blood donors, fifteen males and thirty females; their ages ranged between 35 and 77 yrs (average 54 yrs).

The cases of rheumatoid arthritis were in-patients at the Royal National Hospital for Rheumatic Diseases, who, at the time of the estimation were being treated by rest and physical measures alone. There were 23 males and twenty females; their ages ranged between 30 and 66 yrs (average 51 yrs).

The streptokinase-activated plasmin and antiplasmin levels could not be correlated with the variation of age and sex in either the control or the rheumatoid groups.

The results of the antiplasmin estimations in 38 controls, and 43 cases of rheumatoid arthritis are shown in Table I, which also shows the variation in antiplasmin activity when correlated with the disease state, as expressed by the erythrocyte sedimentation rate (Westergren).

A significant increase over the control antiplasmin levels is found in cases of rheumatoid arthritis ($P = 0{\cdot}001$). This increase is most significant in the more active disease states (*i.e.* sedimentation rate over 50 mm./hr).

The difference in the proteolytic activity of controls and rheumatoid patients is shown in Table II.

TABLE I

ANTIPLASMIN ACTIVITY OF SERUM OF CONTROL AND RHEUMATOID CASES

RESULTS EXPRESSED AS PERCENTAGE OF STANDARD ACTIVITY

Group	Control	Rheumatoid Arthritis			
		Total	Sedimentation Rate		
			0-25	25-50	50+
Number of Cases ..	38	43	10	11	17
Mean per cent. activity	83·5	66·5	71·3	68·3	58·4
Standard Deviation ..	20	26·1	34·1	26·9	26·9
Significance of Variation between Disease Group and Controls	—	0·001	0·20	0·05	0·001

TABLE II

PROTEOLYTIC ACTIVITY OF SERUM OF CONTROL AND RHEUMATOID CASES

RESULTS EXPRESSED IN MICROGRAMS ACID-SOLUBLE "TYROSINE" PER HR

Group	Control	Rheumatoid Arthritis			
		Total	Sedimentation Rate		
			0-25	25-50	50+
Number of Cases ..	45	42	11	12	19
Mean Activity	178	146	134	144	169
Standard Deviation ..	54	43·2	48·9	35·4	42·8
Significance of Variation between Disease Group and Controls	—	0·01	0·02	0·05	0·50

There was a significant decrease in plasmin activity in the rheumatoid cases. Contrary to the antiplasmin findings this decrease in proteolysis bore no definite relation to increased disease activity as expressed by the erythrocyte sedimentation rate.

Comment

Plasmin is one of the main proteolytic enzymes present in blood, and it has been shown to be less sensitive than trypsin to inhibition by serum (Surgenor and others, 1953; Müllertz, 1953). Thus it would seem possible for serum antitryptic levels to be raised without a measurable increase in antiplasmin activity.

Coke found that the antitryptic activity of serum increased with the severity of the disease in rheumatoid arthritis. Though plasmin is less sensitive than trypsin to inhibition by serum, our results show a rise in antiplasmin levels with an increase in the severity of the disease. Thus both inhibitors show a similar rise which can be correlated with the state of the disease. It is of interest, however, that Hammarsten and Jonsson (1954), using chloroform-

activated plasmin preparations, the activity of which was measured by fibrin clot lysis, found no change in either enzyme or anti-enzyme levels in cases of rheumatoid arthritis.

Increase in the serum inhibitor of trypsin was also found by Shulman (1952) to be associated with diseases characterized by tissue destruction. He found that the change in the inhibitor was closely correlated with the sedimentation rate. Holmes and others (1935) reported antitryptic activity in synovial exudates, and suggested that it might prevent tissue damage by protease, liberated from accumulated leucocytes.

As a result of the acute phase of inflammation in the proliferating synovium, fibrinogen makes its appearance in the synovial fluid (Ropes and Bauer, 1953), and this is deposited as fibrin which has plasmin adsorbed on to it (Bidwell, 1953). If no defence mechanism is present, the enzyme is able to lyse the fibrin, and so interfere with the attempt at self-limitation of the inflammation. Increased antiplasmin levels in the serum of rheumatoid arthritis might reflect such a defence process. Thus our findings of increased antiplasmin values in this disease lend support to views on the possible importance of the serum inhibitor. In considering the physiological aspects of this increase, however, the non-specific nature of the response must be taken into account (Burdon, 1950; Guest and others, 1948; Jensen, 1953).

The lowered serum plasmin levels found in cases of rheumatoid arthritis would, at first sight, seem to reciprocate with the increased antiplasmin levels reported; this is not the case, as the lowest proteolytic levels were found in the groups in which the disease was least active; a finding which is quite contrary to the antiplasmin values.

Summary

Estimations of serum plasmin and antiplasmin were carried out in 43 cases of rheumatoid arthritis and 38 control cases.

Serum antiplasmin levels were found to be increased in rheumatoid arthritis, and to vary with the severity of the disease.

Serum plasmin levels appeared to be reduced in rheumatoid arthritis, but were unrelated to the state of the disease as expressed by the sedimentation rate.

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Antiplasmine sérique et plasmine dans l'arthrite rhumatismale

RÉSUMÉ

On a effectué le dosage de la plasmine et de l'antiplasmine sérique chez 43 malades atteints d'arthrite rhumatismale et chez 38 témoins.

On a trouvé que le taux de l'antiplasmine sérique était augmenté dans l'arthrite rhumatismale et qu'il variait avec la sévérité de la maladie.

Le taux de la plasmine sérique paraissait diminué dans l'arthrite rhumatismale mais ne se rapportait pas à l'état de la maladie exprimé par la vitesse de la sédimentation érythrocytaire.

Antiplasmina sérica y plasmina en la artritis reumatoide

SUMARIO

Se determinaron las tasas de la plasmina y de la antiplasmina sérica en 43 enfermos con artritis reumatoide y en 38 testigos.

Se encontró que las cifras de la antiplasmina sérica fuéron aumentadas en la artritis reumatoide y variables según la severidad de la enfermedad.

La cifras de la plasmina sérica parecían reducidas en la artritis reumatoide pero sin relación con el estado de la enfermedad reflejado en la velocidad de la sedimentación eritrocitaria.

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RHEUMATOID ARTHRITIS AND PSORIASIS

BY

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An association between rheumatoid arthritis and psoriasis has been thought to exist for the past 130 years, but its nature is still debatable. There are two main problems:

(*i*) whether the two conditions coincide more frequently than can be explained by chance,

(*ii*) whether "psoriatic arthritis" is a specific disease.

COINCIDENCE OF THE TWO CONDITIONS

(*i*) *Occurrence of Psoriasis amongst Rheumatoid Arthritics.*—The reports available in the English language from Scandinavia or from the U.S.A. are listed in Table I. Although few series are large, their uniformity is striking, and it appears that in both countries some 3 per cent. of all rheumatoid arthritics also suffer from psoriasis. Some of these authors also give the incidence of psoriasis in a control series; these estimates, together with those available for the general population, are shown in Table II; from this it appears that the normal incidence of psoriasis is less than 1 per cent.

TABLE I

OCCURRENCE OF PSORIASIS IN RHEUMATOID ARTHRITICS

Author	Date	Place	Total Cases with Rheumatoid Arthritis	With Psoriasis	
				Number	Percentage
Hench	1935	Rochester, Minn.	65	3	4·6
Dawson and Tyson	1938	New York	1,000	26	2·6
Bauer, Bennett, and Zeller	1941	Boston, Mass.	300	8	2·7
Heinild	1942	Denmark	271	8	3·0
Wassmann	1949	Sweden	1,000	31	3·1
Cecil	1949	New York	930	53	5·6

TABLE II

OCCURRENCE OF PSORIASIS IN CONTROLS

Author	Date	Place	Description	Total Number of Subjects	With Psoriasis	
					Number	Percentage
Dawson and Tyson	1938	New York	Osteoarthritics	>1,000	3	<0·3
Bauer and others	1941	Boston, Mass.	Unspecified	300	2	0·7
Heinild	1942	Denmark	Arthroses other than rheumatoid arthritis	270	0	0
Gahan	1943	New York	General population			At least 1·0
Romanus	1945	Sweden	Mental in-patients	132,675	137	0·1
Forssman	1947		Male conscripts	1,987	2	0·1
			Psychiatric patients	693	10	1·4
Wassmann	1949	Sweden	General medical out-patients	10,000	43	0·4
Ingram	1954	England	General population			1–2

Thus, in both the U.S.A. and Scandinavia, psoriasis seems to be about three times as common in rheumatoid arthritics as in the rest of the population. Reiter and Nørholm-Pedersen (1953) alone disagree, stating that psoriasis was no more frequent in polyarthritis than in other forms of arthritis, but their figures are so inconsistent that it is difficult to follow their reasoning.

(*ii*) *Occurrence of Arthritis amongst Psoriatics.*—The reports available in English are collected in Table III, but unlike those already quoted, are extremely variable. Psoriasis is a definitive disease, whereas "arthritis" is a generic term, and its incidence in psoriatics depends on its definition; in Table III this varies from asking patients whether they had ever suffered from "arthritis" and recording the answers without clinical confirmation (Lane and Crawford, 1937), to a strict definition of "psoriatic arthritis" (Epstein, 1939). No conclusion about the incidence of *rheumatoid* arthritis amongst psoriatics can therefore be drawn from these reports.

Romanus (1945), in a more specific report, found that 2·2 per cent. of a series of psoriatics developed a polyarthritis severe enough to require admission to hospital, but after calculating the risk of being admitted to hospital for polyarthritis among the whole population, he concluded that "no increased risk of developing chronic polyarthritis is found for psoriatic patients".

Investigation.—An attempt was made to estimate the incidence of psoriasis in all the rheumatoid arthritics who attended the Department of Physical Medicine at The London Hospital during the last three months of 1953. The major disability in those with both diseases was the arthritis, and since no rheumatoid arthritic is ever discharged, it is unlikely that those who also had psoriasis were selected. Only those with a definite diagnosis of rheumatoid arthritis or intermittent hydrarthrosis were included, and in each case the diagnosis of psoriasis was confirmed by a dermatologist.

TABLE III

OCCURRENCE OF ARTHRITIS IN PSORIATICS

Author	Date	Place	Definition of Arthritis	Total Number of Subjects	With Psoriasis	
					Number	Percentage
Coste and Forestier	1935	France				0·5
Giordano	1939	Italy				0·3 0·5
Lane and Crawford	1937	Boston, Mass.	"Arthritis"	231	74	32
Epstein	1939	California	Arthritis with "reasonably synchronous activity"			<1·0
Ayres, Becker, Chargin, Cornbleet, Fox, Madden, and O'Leary	1941	Los Angeles	"Arthritis"	707	85	12
		Chicago	"Arthritis"	200	26	13
		New York	"Arthritis"			<0·2
		Dallas	"Arthritis"	108	1	0·9
		Minnesota	"Arthritis at some time"			25
		Minnesota	"Arthritis"			*15
Brunsting	1943	Minnesota	"True psoriatic arthritis"			15
O'Leary	1943	Minnesota	Arthritis, chronic infective, senescent or psoriatic			12
Romanus	1945	Sweden	Polyarthritis requiring hospitalization	768	17	2·2
Leczinsky	1948		Polyarthritis	543		6·8
Vilanova and Piñol	1951	Spain	"Psoriatic arthritis" (including "algic" form)	214	54	25
Ingram	1954	England	"Arthritis"	1,346		7

* Including 12 per cent. of infectious and 3 per cent. of psoriatic origin.

TABLE IV

OCCURRENCE OF PSORIASIS IN RHEUMATOID ARTHRITICS

(PRESENT SERIES)

Sex	Joint Condition	Total Number	With Psoriasis	
			Number	Percentage
Female	Rheumatoid arthritis	298	12	
	Intermittent hydrarthrosis	3	1	
	Total	301	13	4·3
Male	Rheumatoid arthritis	123	5	
	Intermittent hydrarthrosis	—	—	
	Total	123	5	4·1
Total		424	18	4·2

Results.—These are shown in Table IV, where it may be seen that:

(1) The overall incidence of psoriasis was 4·2 per cent.

(2) The incidence in males and females was the same.

However, in some of the psoriatics the arthritis was mild and so limited that it was questionable whether a patient with uncomplicated rheumatoid arthritis of this degree would have attended the department. Even if these cases are omitted, there remain nine psoriatics among 297 female arthritics (3·0 per cent.), and four among 122 male arthritics (3·3 per cent.), the mean incidence being 3·1 per cent.

Conclusion.—The Scandinavian and American reports agree that the incidence of psoriasis in rheumatoid arthritis is about 3 per cent., whereas among the rest of the population it is less than 1 per cent.; in this London series also, psoriasis occurred in between 3 and 4 per cent. of all rheumatoid arthritics, both sexes being equally affected.

Is Psoriatic Arthritis a Distinct Disease?

The term psoriatic arthritis, which has been used to cover a great variety of conditions, should be restricted to describing, first, an arthritis which is characterized by physical signs as well as pain, and secondly one which is "allied to rheumatoid arthritis or one of its sub-varieties, ankylosing spondylitis or Still's disease" (Dawson and Ragan, 1946). Pain alone is not adequate evidence of arthritis, though it has been considered so by Lane and Crawford (1937), Jungmann and Stern (1944) and Vilanova and Piñol (1951), and though the term has been applied to the association of psoriasis with osteo-arthritis (Gibson, 1948; Jeghers and Robinson, 1937; O'Leary, 1943), and gout (Barber, 1938), its occurrence in these conditions is merely coincidence (Dawson and Ragan, 1946).

Having accepted that the incidence of psoriasis in rheumatoid arthritics is greater than in the general population, there remains the problem whether the patient with both diseases has classical rheumatoid arthritis, or whether the arthritis with psoriasis is sufficiently different to be classified as "psoriatic arthritis". When the two conditions occur together, the arthritis "may assume certain unusual characteristics" (Dawson and Tyson, 1938), and it is on these unusual characteristics that the various definitions of "psoriatic arthritis" have been based. Since so many have been suggested and so few agree, it is of interest to consider each of the "unusual characteristics" in more detail.

(1) *The onset of arthritis follows the onset of psoriasis.*—Most authorities have found that the onset of arthritis either follows or coincides with that of psoriasis, the psoriasis rarely appearing after the arthritis (Brunsting, 1943; Garrod and Evans, 1924; Graham, 1953; Hench, 1927, 1935; Jungmann and Stern, 1944; Nunemaker and Hartman, 1950; Sherman, 1952; Sterne and Schneider, 1953; Vilanova and Piñol, 1951). However, since psoriasis starts typically before the age of 30 (Vickers, 1950; Romanus, 1945), and the mean age of onset of rheumatoid arthritis is between 40 and 45 years (Davidson, 1948; see also below), it follows that the skin condition will normally precede the arthritis, whether or no the two conditions are related. This point is made by Reiter and Nørholm-Pedersen (1953).

(2) *The severity of both diseases varies synchronously.*—This has frequently been noted (Brunsting, 1943; Epstein, 1939; Garrod and Evans, 1924; Gibson, 1948; Graham, 1953; Hench, 1927, 1935; Hunt, 1932; Jeghers and Robinson, 1937; Nordin, 1934; Nunemaker and Hartman, 1950; O'Leary, 1943; Vilanova and Piñol, 1951), and it is considered by many to be essential to the diagnosis of "psoriatic arthritis". It has also been found that whereas treatment of the arthritis had no effect on either condition, treatment of the psoriasis relieved both (Franks and Wallace, 1942; Hench, 1935; Jungmann and Stern, 1944). On the other hand, others found little or no synchronous activity in typical cases

(Barber, 1938; Clarke, 1950; Sherman, 1952; Wassmann, 1949), whilst Dawson and Tyson (1938) found it in half their cases and Reiter and Norholm-Pedersen (1953) in one-third.

Synchronism is nearly always the patient's subjective impression, so that increased psoriatic activity may merely direct attention to the arthritis, or in common with other diseases, it may increase the arthritic activity, but in each case the parallel fluctuations are probably not an effect specific to psoriasis.

(3) *Involvement of the terminal inter-phalangeal joints.*—It has been stated that when both diseases co-exist, the terminal inter-phalangeal (TIP) joints of the hands and feet are frequently affected, whereas this is rare in uncomplicated rheumatoid arthritis (Barber, 1938; Bauer, Bennett, and Zeller, 1941; Brunsting, 1943; Gibson, 1948; Graham, 1953; Hench, 1935; Hunt, 1932; Jungmann and Stern, 1944; Mattingly, 1953; Nordin, 1934; Nunemaker and Hartman, 1950; Plenk, 1950; Sherman, 1952; Shlionsky and Blake, 1936; Sterne and Schneider, 1953; Vilanova and Piñol, 1951). This arthritis is frequently associated with psoriasis of the nails, and according to some reports occurs only when the corresponding nail is affected and *vice versa* (Nunemaker and Hartman, 1950; Plenk, 1950; Sherman, 1952).

It is frequently difficult to distinguish between specific TIP arthritis and Heberden's nodes, for although these are usually a primary condition, they are also the final result of any arthritis of the TIP joints. If a specific arthritis is seen in the acute stage with soft tissue involvement, the diagnosis is clear, but it is far from easy to differentiate the later stages from independent Heberden's nodes. Hench (1935) suggested that TIP arthritis is probably specific if (*a*) the patient is too young for Heberden's nodes, and (*b*) the TIP joints of the toes are also affected. Unfortunately, most of the patients in this series were old enough to have developed Heberden's nodes in any case, and the toes of almost every patient seen in the department are so deformed that it is impossible to say whether or no they are involved in a specific arthritis.

Since we are told that in psoriatic arthritis, affection of the TIP joints is typical, it is probable that any form of TIP arthritis in these patients is considered to be part of the syndrome; on the other hand, in uncomplicated rheumatoid arthritis, we are told that these joints are rarely involved, so that TIP arthritis, when found, is considered to be an independent symptom. It is possible, therefore, that the strict association of TIP arthritis with psoriatic, but not rheumatoid, arthritis is not always justified; this is borne out by Bauer and others (1941), who found TIP arthritis frequently in uncomplicated rheumatoid arthritis, by Cecil (1949), who considered that in the presence of psoriasis, TIP arthritis was "accidental", and by the present finding that the incidence of TIP arthritis in this series was little different from that of Heberden's nodes in a control series of uncomplicated rheumatoid arthritics.

(4) *Bone destruction.*—Arthritis mutilans is usually associated with psoriasis, but does occur without (Graham, 1953; Jonsson, 1949; Mather, 1954), but lesser degrees of destruction of the bones of the hands and feet have been more specifically associated with psoriasis (Brunsting, 1943; Fawcitt, 1950; Gibson, 1948; Sherman, 1952; Sterne and Schneider, 1953). The destruction affected mainly the distal ends of the bones, and in some cases there was associated widening of the articular surface of the proximal end of the adjoining bone, often with indentation (Fawcitt, 1950; Gibson, 1948). This limited destruction is not recorded in the absence of psoriasis, though presumably it must be a stage in the development of arthritis mutilans, with or without skin involvement.

(5) *Reversible nature of arthritis.*—Some authors have found that, particularly in the early stages, the arthritis may undergo complete remissions rarely seen in uncomplicated rheumatoid arthritis (Brunsting, 1943; Garrod and Evans, 1924; Graham, 1953; Nordin, 1934; Sherman, 1952). On the other hand, Jungmann and Sterne (1944) state that once affected, the joint never becomes normal again.

(6) *Association with intermittent hydrarthrosis.*—Barber (1938) and Garrod and Evans (1924) found that psoriasis was often associated with intermittent hydrarthrosis, but later authors have not confirmed this observation.

(7) *Sex incidence.*—According to Sherman (1952) and Vilanova and Piñol (1951) "psoriatic arthritis" is commoner in males, whereas Epstein (1939) stated that the sex distribution was equal. However, since none of these authors defined the nature or size of the population from which their series were taken, no conclusion can be drawn. Romanus (1945) found that, in each of various reports, the sex distribution of psoriatic arthritis was always the same as that of the rest of the patients seen by each author, and both in the present series and in that of Reiter and Nørholm-Pedersen (1953) the incidence was equal in both sexes.

The disagreement as to which of these unusual characteristics are found in "psoriatic arthritis" is reflected in the many definitions summarized in Table V (overleaf).

Many of these reports are based on single cases or on very small series, so that minor differences might be expected, but no clear picture of even the major features emerges. The greatest agreement is found on the earlier onset of the psoriasis, the distribution of the arthritis, and the frequency of bone destruction; the commonest single feature is arthritis of the TIP joints with associated psoriasis of the corresponding nails, and some would restrict the term "psoriatic arthritis" to cases in which the arthritis is confined to these joints (Bauer and others, 1941; Mattingly, 1953; Nunemaker and Hartman, 1950; Plenk, 1950). Nevertheless, apart possibly from the limited bone destruction, the remaining characteristics are either not specific or subjects of disagreement.

DESCRIPTIO ARTHRIT

Author	Date	Psoriasis precedes or is Coincidental with Onset of Arthritis	Synchronous Variation	Improvement of Arthritis only follows that of Psoriasis	Involvement of TIP Joints	Psoriasis of Nails	Pso Nail Distr TIP	ent of oints
Barber	1938		No		+	+		
Bauer and others	1941				+ Only			
Brunsting	1943	+ Usual	+ At first		+ At first			
Cecil	1949	+ Usual			Accidental only			
Clarke	1950	No	No					s and only
Dawson and Tyson (quoting others)	1938	+	+		+	+		
Epstein	1939		+					o
Fawcitt	1950	+						o
Franks and Wallace	1942	+		+				
Garrod and Evans	1924	+	+					
Gibson	1948		+		+	+		
Graham	1953	+ Usual	+		+	+		
Hench	1927	+	+					
	1935	Coincident	+	+	+	+		-
Hunt	1932		+		+	(+)		
Jeghers and Robinson	1937	+	+					
Jungmann and Stern	1944	+		+	+	+		etimes
Mattingly	1953				+ Only			
Nordin	1934	+	+		+	+		-
Nunemaker and Hartman	1950	+	+		+ Only	+		-
O'Leary	1943		+		+	+		
Plenk	1950				+ Only	+		+
Sauer	1951	+						
Sherman	1952	+	Unusual		+	+		+
Shlionsky and Blake	1936	+			+	+		
Sterne and Schneider	1953	+						
Vilanova and Piñol	1951	+	+ Usual	Never				
Wassmann	1949		Unusual		Unusual			

If psoriatic arthritis is to be accepted as a distinct naturally occurring disease, it should be constantly and clearly distinguishable from rheumatoid arthritis, though allied to it; some authors, in describing a series, found that certain patients also had features typical of rheumatoid arthritis, and explained it by suggesting that these patients had both psoriatic and rheumatoid arthritis (Sterne and Schneider, 1953;

DESCRIPTI ARTHRITIS

Frequency of Intermittent Hydrarthrosis	Complete Remissions of Arthritis	Type of Psoriasis	X Ray			Arthritis Mutilans
			General	Destruction of Bone	Widening of Articular Surface	
+ Often						
	+ At first		= Rh. A. At first	+ Late		
				+		+
		Waxy				
			= Rh. A. At first	+	+	
+ Often	+					
				+	+	
	+			+ Sometimes		
	+			+		
	Never		General Osteoporosis	+	+	+
				+		+
	+ At first			+		
				+		+
			No General Osteoporosis	+		
						Unusual

Fawcitt, 1950), but this is too fanciful a concept to form serious evidence for the separate existence of psoriatic arthritis.

It is probable that the desire to distinguish psoriatic arthritis from rheumatoid arthritis originated in the observation that the two conditions were more frequently associated than can be explained by chance. Since the incidence of psoriasis in

rheumatoid arthritics is about three times that of the general population, then either:

(*a*) One-third of the cases in which the two diseases co-exist should have unexceptional rheumatoid arthritis (cases of chance association), and the other two-thirds should have a distinct arthritis;

or (*b*) all cases with both diseases should have the distinct arthritis, *i.e.* the presence of psoriasis constantly alters the form of the arthritis.

Analysis of this Series.—The series consists of the eighteen cases considered in the first part (Table IV) and two others who first attended in 1954. The characteristics of their disease are considered under the headings used above. Some comparisons have been made with a small control series of 49 women and seventeen men with uncomplicated rheumatoid arthritis.

(1) *Time relationship.*—Since there are only five men, the series is treated as a whole, and the mean age at onset of arthritis is seen to be 41·2 yrs (Table VI), or, if the mild cases are omitted, 36·4 yrs. In the control series it was 44·9 ± 1·47 yrs in the women, and 44·6 ± 3·12 yrs in the men, and is thus probably not significantly altered by the presence of psoriasis. It may be calculated from the data given by Reiter and Nørholm-Pedersen (1953) that the mean age at onset of the arthritis in their psoriatics was 38·6 yrs. Although the arthritis appears to start later than the psoriasis, the small difference is not statistically significant. Unless patients had forgotten earlier attacks, or gave a history too vague to diagnose in retrospect, the surprising feature is the late onset of the psoriasis.

(2) *Synchronous variation.*—Roughly half showed synchronous variation, though it was not always constant.

(3) *Involvement of TIP joints.*—Fig. 1 (opposite) shows the distribution of affected joints in all except the five very mild cases; it is seen that the TIP joints are involved in about one-third, but that most other joints of the body, except the hip, are involved at least as frequently; there was no relative sparing of the metacarpo-phalangeal joints, as described by Sherman (1952). Fig. 2 (opposite) shows the distribution of affected joints in the control series; some had arthritis of the TIP joints, usually in the form of Heberden's nodes, and this column is only cross-hatched, whereas in Fig. 1 it is blacked in, regardless of the exact appearance of the joints.

It is striking that the proportion of cases with involvement of these joints is so similar in both the psoriatics and non-psoriatics; moreover the general distribution of the arthritis is practically identical. Reiter and Nørholm-Pedersen (1953), in a similar study, concluded that there were differences, but the frequency distribution in their psoriatics was almost the same as that in Figs 1 and 2, while their control series appeared atypical.

TABLE VI
DETAILS OF INDIVIDUAL PATIENTS
(PRESENT SERIES)

Degree of Disease	Patients	Age at Onset of Arthritis	Age at Onset of Psoriasis	Period by which Psoriasis precedes or follows Arthritis	TIP Joints Involved	Other Small Joints of Hands (including Wrists) Involved	Large Joints Involved	Psoriasis of Finger Nails	Synchronous Variation	Bone Destruction in Hands	Radiological Widening of Articular Margin
Severe	1	30	23	7 yrs	+	+	+	+	–	–	–
	2	25	14	11	+	+	–	+	–	+	+
	3	40	38	2	–	+	+	–	+	–	–
	4	59	61	– 2	–	–	+	+	–	–	–
	Women: 5	69	58	11	–	+	+	±	+	–	–
	6	21	21	A few weeks	+	+	+	+	+	–	–
	†7	18	22	– 4 yrs	–	–	+	–	–	–	–
	8	54	67	–13	–	+	+	+	(+)	–	+
	*9	24	40	–16	+	+	+	–	–	+	–
	10	50	50	A few months	+	+	+	+	–	+	+
	11	30	33	– 3 yrs	+	+	+	–	+	+	+
	Men: 12	18	17	1	–	–	+	+	+	–	–
	13	30	30	Coincidental	+	+	+	+	+	+	+
	14	37	35	2 yrs	–	+	+	+	–	–	–
	Total ..	36·4 ±4·23	36·1 ±4·62								
Mild	15	64	17	47 yrs	–	+	–	–	–	–	–
	16	56	53	3	–	+	–	+	+	–	–
	Women: 17	49	32	17	–	+	–	+	+	–	–
	18	49	45	– 4	–	+	–	+	–	–	–
	19	43	43	A few weeks	–	+	+	+	–	–	–
	Men: 20	57	51	6 yrs	–	+	–	–	–	–	–
All Cases		41·2 ±3·59	37·5 ±3·53								

* Arthritis mutilans. † Intermittent hydrarthrosis.

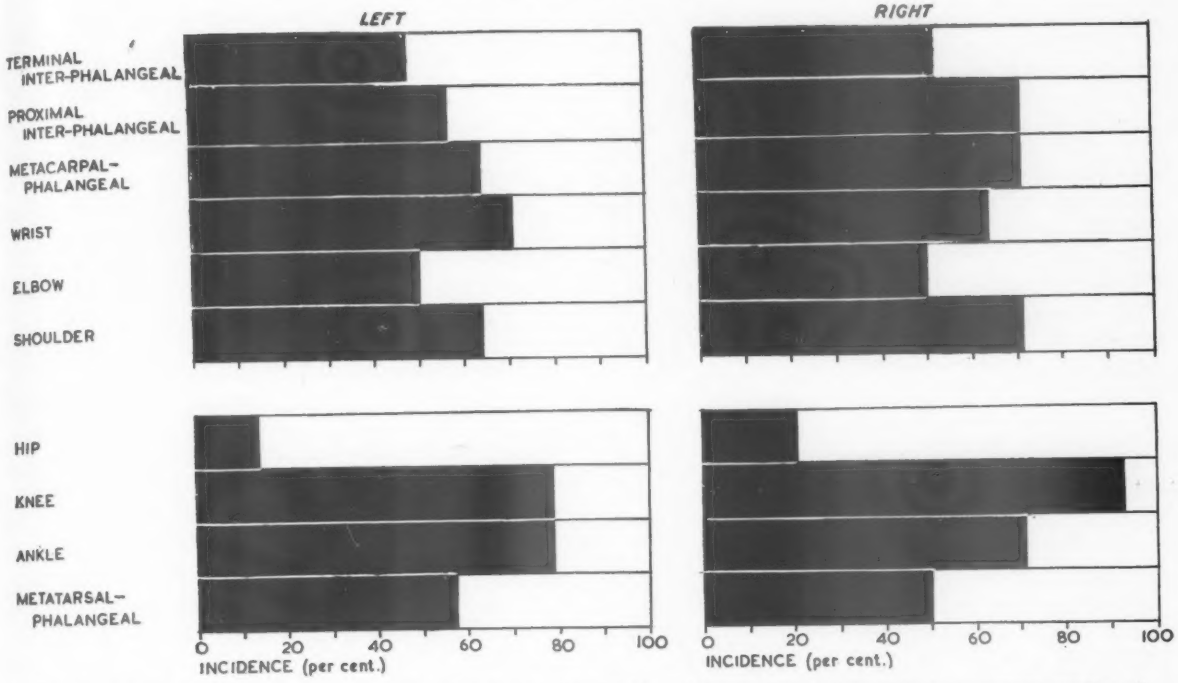

Fig. 1.—Distribution of arteries in fourteen severe rheumatoid arthritics with psoriasis Blocks indicate percentage number of patients with involvement of each joint.

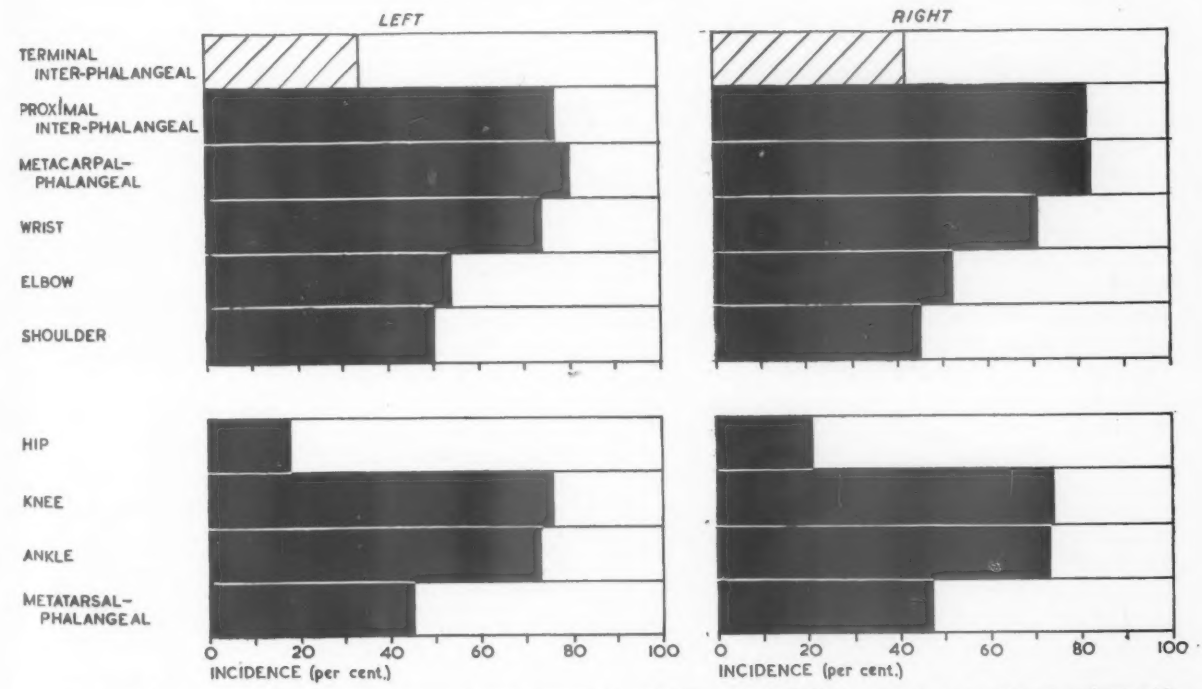

Fig. 2.—Distribution of arthritis in 66 uncomplicated rheumatoid arthritics. Blocks indicate percentage number of patients with involvement of each joint.

(4) *Bone destruction.*—Five cases (one-third of the series, after discounting the mild cases) showed radiological destruction of the long bones of the hands, whereas no destruction was found clinically in the controls.

(5) *Reversible nature of arthritis.*—The period of observation was too short to observe this, but it was not mentioned in any history, and is not therefore a comparable feature.

(6) *Association with intermittent hydrarthrosis.*—In this series (Table IV) no man had this condition, but it was seen in three of the 301 women in the non-psoriatic group, and one in the nine psoriatics; both groups are too small to make this apparent difference significant.

No case of psoriasis was seen in 33 men and ten women attending with ankylosing spondylitis.

(7) *Sex incidence.*—Three times as many women were seen as men, and in both sexes the incidence of psoriasis was between 3 and 4 per cent.

Discussion

If "psoriatic arthritis" were a naturally occurring disease distinct from rheumatoid arthritis, one would expect at least two-thirds of this series to show a uniform pattern clearly distinguishable from that of rheumatoid arthritis, but this is far from being the case. Nor do any of the arthritic patterns (Table VI) satisfy the criteria suggested for "psoriatic arthritis". Whenever the TIP joints appeared to be involved, other small joints of the hands were also affected, and usually some of the large joints elsewhere as well, nor was the distribution of the arthritis appreciably different from that of uncomplicated rheumatoid arthritis. Half showed some synchronous variation, but it was often neither striking nor exact. The two most characteristic features were the high incidence of bone destruction, and the high frequency of psoriasis of the nails, though this was by no means necessarily associated with arthritis of the corresponding TIP joint.

In Table VII the incidence of the main characteristics in this series is compared with that in the only other unselected series, and there is fair agreement except that there is no mention of bone destruction. It seems possible, therefore, that the high incidence of bone destruction in the present series is not strictly representative, and that this character should not be considered the distinctive feature of a distinct "psoriatic arthritis" without further confirmation.

Conclusion

It does not appear justifiable to consider "psoriatic arthritis" as a distinct naturally occurring syndrome. The descriptions that have been suggested are based on certain arbitrarily selected characteristics, but since no single one can account for the excess of rheumatoid arthritics who also have psoriasis, they appear to serve no useful purpose. One must therefore conclude, as did Dawson and Tyson (1938) that the most that can reasonably be claimed is that rheumatoid arthritics seem to be unusually prone to psoriasis, and that when they have both diseases, the arthritis may often take one of its less usual forms; the commonest of these is bony destruction in the hands, the psoriasis also appears unusual in its late onset, and in the high incidence of nail involvement.

Since the term "psoriatic arthritis" varies so widely in its meaning from one writer to another, it should be discarded, but, in recognition of the peculiar frequency with which psoriasis occurs in rheumatoid arthritics and the unusual forms that the arthritis may take, it would be well always to specify that the patient suffering from both diseases has "rheumatoid arthritis *with* psoriasis".

Summary

(1) The incidence of psoriasis in a series of rheumatoid arthritics was found to be between 3 and 4 per cent.

(2) This incidence was the same in both men and women.

(3) In the presence of psoriasis, the arthritis may assume unusual forms, but these are too variable to permit the designation of a "psoriatic" as opposed to "rheumatoid" arthritis.

(4) It is recommended that the term "psoriatic arthritis" be dropped.

TABLE VII

SPECIAL CHARACTERISTICS OF RHEUMATOID ARTHRITIS WITH PSORIASIS

Author	Date	Percentage showing			Total Number of Cases
		TIP Arthritis	Synchronous Variation	Psoriasis of Nails	
Dawson and Tyson	1938	23	54	69	26
Bauer and others	1941	62	—	77	26
Reiter and Nørholm-Pedersen ..	1953	—	31	—	111
Present Series	Complete	35	40	65	20
	Restricted	50	43	64	14

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Arthrite rhumatismale et psoriasis

RÉSUMÉ

(1) On a trouvé que la fréquence du psoriasis dans une série des cas d'arthrite rhumatismale était de 3 à 4 pour cent.

(2) La fréquence était la même chez les hommes et les femmes.

(3) En présence du psoriasis, l'arthrite peu revêtir des formes peu habituelles, mais si variables qu'on ne peut pas opposer l'arthrite "psoriasique" à la "rhumatismale".

(4) On recommande l'abandon du terme "arthrite psoriasique".

Artritis reumatoide y psoriasis

SUMARIO

(1) Se determinó la frecuencia de psoriasis en una serie de casos de artritis reumatoide, siendo esta de un 3 a 4 por ciento.

(2) Esta frecuencia dué la misma en ambos sexos.

(3) En presencia de soriasis, la artritis pueded asumir formas poco habituales pero tan variables que no se puede oponer una artritis "psoriásica" a la reumatoide.

(4) Se aconseja el abandono del término "artritis psoriásica .

EMPIRE RHEUMATISM COUNCIL

EIGHTEENTH ANNUAL REPORT

The eighteenth annual report of the Empire Rheumatism Council was presented by the Chairman, Dr. W. S. C. Copeman, at the Annual General Meeting held on April 27, 1955, at the Royal College of Surgeons.

The Chairman first recorded with regret the loss of a most distinguished colleague, Dr. Frank D. Howitt, whose wise and able guidance would be sadly missed, and of the Rev. H. Heberden, a direct descendant of Dr. W. Heberden, the distinguished 18th-century physician, after whom the Heberden Society is named.

During the year under review a further meeting had taken place with the Minister of Health to amplify what had previously been presented by the E.R.C. Deputation. The Council's views had been favourably received and the Minister had promised that, in the new Ministry Circular regarding senior appointments, Rheumatology would be mentioned as a subject in which a senior medical registrar could be employed during his training. This was considered an important step towards the ultimate recognition of Rheumatology as a medical specialty.

The Rheumatism Research Centre in the University of Manchester had been started in 1947 as an experimental ten-year scheme financed by the Nuffield Foundation; the Empire Rheumatism Council's action in financing the establishment of a Chair of Rheumatology in the University of Manchester had been largely instrumental in transforming the original experimental scheme to an established department within the university. During 1954 the Nuffield Foundation had offered the university a further grant of £70,000 to develop research in rheumatism, so providing the professor with the assured support of a well-endowed department.

Research.—Since the departure of Dr. A. A. Henly, the laboratory at the Hospital of St. John and St. Elizabeth had not remained idle, but had been used for follow-up work by Miss I. H. M. Muir, one of the Empire Rheumatism Council Fellows, new equipment and apparatus having been installed.

The following reports had been received from the E.R.C. Fellows:

(1) From Dr. Norymberski, Director of Medical Research within the Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases:

"Dr. J. K. Norymberski, Miss J. I. Appleby, Mr. G. Gibson, Dr. Jean McKenna, Mr. R. D. Stubbs, and Dr. G. F. Woods, have carried out the following work at the Chemical Research Laboratory of the Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases.

"The methodology of steroid analysis has received further attention. The combination of reductive and oxidative operations performed on the analytical sample (*e.g.* urine or urine extract) was found to provide a simple means of:

(*i*) estimating all 17-hydroxycorticosteroids (17-OH CS);
(*ii*) selectively estimating 21-deoxy-17-hydroxy-20-oxosteroids;
(*iii*) partially characterizing or, in some cases, identifying individual 17-OH CS.

"The determination of 21-deoxy-17-hydroxy-20-oxosteroids in the urine disclosed a certain type of adrenocortical dysfunction which was found in the adrenogenital syndrome, but, contrary to previous indications, not in rheumatoid arthritis.

"Work was continued on the chemistry of steroid sulphates. Conditions were found for the solvolytic fission of such compounds. Methyl esters of steroid sulphates were prepared; this new and interesting class of compounds was studied in some detail. Synthetic work was commenced with the aim to prepare new derivatives of steroid hormones and to test their biologic activity."

(2) From Prof. A. W. Pickering, Director of the Medical Unit at St. Mary's Hospital, Paddington:

"Miss I. H. M. Muir's work in the past year has been devoted to the study of connective tissue polysaccharides; firstly, because relatively little is known about their structure in normal or diseased states, and, secondly, because recent isotopic work has shown that their turnover rates are very much higher than that of the collagen of the same tissues. It therefore seems a possibility worth investigating that it is the metabolism of polysaccharides that is deranged in connective tissue diseases. Work was therefore undertaken on the following lines:

(*i*) Assay of Glyco-sulphatose.—An accurate and, if possible, rapid method of assay would allow such an enzyme to be identified and its distribution in normal and diseased tissues to be determined. The assay depends on the estimation of inorganic sulphate in tissue homogenates. A method that will estimate 5-25 μg. has been developed. The activity of cell-free homogenates, so far assayed, is small, when pure chondroitin sulphate or heparin were used as substrates.

(*ii*) Improved Methods of preparing and identifying Acidic Polysaccharides.—

(*a*) Nearly all current methods of preparing acidic polysaccharides cause some degree of depolymerization because contaminating protein is extremely difficult to remove. An improved method of preparing chondroitin sulphate, heparin and hyaluronic acid has been found, which makes use of their insoluble salts with basic dyes. These can more easily be freed of contaminating protein.

(*b*) Acidic polysaccharides have been identified after

paper electrophoresis or chromatography by staining with metachromatic dyes. A method which greatly increases the sensitivity of their stain has been found, so that 0·5 μg. can be detected on paper.

(*iii*) Investigation of the Structure of Undegraded Chondroitin Sulphate.—The difficulty of obtaining undegraded polysaccharides from connective tissue has so far prevented much investigation of their structure. Depolymerization of polysaccharides, which is a facile and irreversible process, may account for some of the physical changes of diseased connective tissue. The depolymerization, homogeneity, and composition of chondroitin sulphate of high molecular weight is being investigated. Preliminary work has shown that it may not be a simple polymer of the degraded material, and that in the tissues at least part of the chondroitin sulphate may be combined with peptide or protein. It has been found that the quantity of chondroitin sulphate which can be extracted from cartilage after very careful digestion with papain is at least five times greater than that obtained by methods which do not break down protein to any great extent. This material has a very low viscosity and therefore a relatively small molecular weight. It is only partially precipitated by cobaltic hexamine chloride which precipitates high molecular weight chondroitin sulphate quantitatively from dilute solutions. The effect of purified papain on cartilage and on highly polymerized chondroitin sulphate is being investigated.

Through the generosity of Geigy Pharmaceutical Co. Ltd., it had been possible to found a "Geigy Travelling Fund" to finance travelling fellowships for (*a*) senior medical graduates interested in rheumatism, for short periods, and (*b*) relatively junior men or women (*e.g.* of registrar or senior registrar level, but not excluding non-medically qualified personnel) for a minimum travelling period of nine months with a maximum of one year. The conditions governing these Fellowships had been based upon those of the Medical Research Council.

The first Geigy Travelling Fellow to be appointed was Dr. Malcolm Thompson of the Rheumatic Unit, Northern General Hospital, Edinburgh, who would be leaving for the U.S.A. in November next, to continue his studies in America under Prof. Walter Bauer at the Massachusetts General Hospital and Harvard Medical School, Boston.

A second fellowship has been awarded to Dr. J. Sharp, Lecturer in Rheumatic Diseases, Manchester University, who will visit the U.S.A. for a period of eight or nine months commencing in the spring of 1956, to study certain aspects of ankylosing spondylitis in New York, possibly under Dr. R. Freyberg.

A third fellowship has been awarded to Dr. J. Ball, also of Manchester University Rheumatism Research Centre, for a three-months' educational tour in the United States to enable him to visit leading educational institutions there during 1955.

The council had decided to continue to support Dr. E. Wittkower, Assistant Professor of Psychiatry in McGill University, Canada, in his "Study of Rheumatoid Arthritis in Two Contrasting Communities". This study had been planned to investigate the reciprocal relationships between the rheumatic patient and his illness and between the patient and his social environment, as the disease ran its course over a period of years.

The nine selected centres in England and Scotland had continued the therapeutic trial of cortisone acetate and aspirin in cases of established rheumatoid arthritis of all grades of severity. Although the results of the first year's treatment were not yet fully analysed, a preliminary analysis made in 1954 showed that there was little obvious difference between the two methods over a period of one year. This conclusion might not be valid for the analysis of the whole series which was expected to be presented at a meeting of the Heberden Society with an analysis of the concurrent *x*-ray changes.

In the hydrocortone trials referred to in the last report, which had been carried out at ten selected centres in England and Scotland, there was unanimity of opinion that some patients appeared to respond well, and others not at all; that a good effect was perhaps more commonly seen in rheumatoid arthritis than in osteo-arthritis or soft tissue lesions; but that relapses after treatment were also very common.

Dr. Margaret Holroyde had been conducting a small-scale survey to determine the number of patients with various types of rheumatic disease referred to a typical physiotherapy department of a suburban hospital, serving a fairly well-defined light industrial and semi-rural area. It had been found that 78 per cent. of patients had been referred because of their rheumatism. Just under one-quarter of them had rheumatoid arthritis (152 new cases occurring in the year) and one-third had osteo-arthritis, most of the latter being "middle-aged housewives". These detailed figures provided valuable factual data for the Regional Hospital Board authorities in planning the long-term investigation and treatment of this group of diseases.

Certificates of good order had been received in all instances where equipment and apparatus had been purchased by the council for various rheumatism centres out of the Hormonal Research Equipment Fund.

In view of the importance of the American Rheumatism Association Meeting, held in California in June, 1954, the council had sent Dr. H. F. West, of Sheffield University, as a delegate. In addition to reporting on the M.R.C. trials, Dr. West had also given a resumé of the long-term cortisone-aspirin trials.

Education.—The Education Sub-Committee of the Scientific Co-ordinating Committee had met regularly, under its chairman, Dr. W. S. Tegner. The report of the Royal College of Physicians' Committee on Chronic Rheumatic Diseases had been fully discussed. Reports received from selected Regional Hospital Boards on facilities, or lack thereof, for treatment, diagnosis, and research were condensed into a concise tabulated statement, which was circulated to professors of medicine, senior administrative medical officers of Regional Hospital Boards, and to directors and deans of postgraduate schools. It was felt that the furnishing of such information to these officials might help to emphasize the need for the inauguration or increase of such facilities.

From this information there had emerged a discussion on specialist training in rheumatism, and the sub-committee had agreed that it was desirable to define clearly the council's policy in this respect. It was affirmed that the registrar level was not a suitable stage

for specializing in rheumatism; that such specialized training should not commence until the senior registrar level, or above; that it would be more satisfactory if junior posts in rheumatism were annual, and senior house officers appointed for two-year periods at registrar level; and that it would be most valuable to have some form of orthopaedic training at senior house surgeon's level by an interchange in centres with both orthopaedic and rheumatic units.

Over 15,000 free copies of a handbook on rheumatoid arthritis has been distributed. It was not designed for issue direct to patients, but for general practitioners who might pass them to patients at their discretion. Five impressions had been printed and bulk quantities had been supplied to the Northern Ireland General Health Services Board, America, the New Zealand Rheumatism Council and Grey Hospital, the West Indies, and even behind the "iron curtain". Permission had been granted to a health education journal in Yugoslavia to translate the text for local reproduction. Further copies would gladly be supplied gratis, on application to the General Secretary of the E.R.C.

The popularity of this Rheumatoid Arthritis Handbook had led to the planning of a pictorial handbook for patients suffering from osteo-arthritis.

It had been felt that it might be advantageous to organize refresher courses at consultant level, and Sir Francis Fraser (Director of the British Post-Graduate Medical Federation) had agreed that such a course should be held under the aegis of the University of London; the first Consultants' Three-day Lecture Course had already been held at the Middlesex Hospital.

The Heberden Society had arranged a comprehensive series of educational lectures and demonstrations.

To stimulate interest in the rheumatic field, the Council had made an annual grant of £25 each to the libraries of the British Medical Association and the Royal Society of Medicine, for the purchase of books on rheumatism, arthritis, etc. Suitable book-plates had been inserted in all books so purchased, indicating their source.

The *Annals of the Rheumatic Diseases* continued to be the official medium through which the activities of the Empire Rheumatism Council, the Heberden Society, the British Branch of the European League against Rheumatism, and kindred organizations in Europe and America, were published for the benefit of those interested in the field of rheumatology throughout the world.

During the year, Dr. C. W. Buckley had retired from the post of chief editor of the *Annals of the Rheumatic Diseases*, in which capacity he had served since the foundation of the Journal in 1936. The Chairman had felt proud to be elected to succeed him as editor, and had been encouraged to accept this onerous office in the knowledge that his burden would be eased by the co-operation of Dr. Oswald Savage as assistant editor, and of a hard-working and learned editorial committee.

Correspondence had taken place during the year with leading American rheumatologists regarding the possibility of the foundation of a rheumatism journal in the U.S.A. No definite decision had been arrived at.

Commonwealth.—Close collaboration had been maintained with the council's affiliated branches, and vigorous steps were being taken to stimulate teaching, research, and treatment.

Dr. J. E. Grant had been nominated by the Canadian Arthritis and Rheumatism Council to serve on the Scientific Co-ordinating Committee and Commonwealth Sub-Committee, as their liaison officer. Dr. Watson, the Australian representative, had been recalled to Australia, and the loss of the benefit of his valuable advice was much regretted.

The Chairman had accepted invitations from the Australian Rheumatism Council and the University of Sydney, and from the New Zealand Rheumatism Council and the New Zealand Ministry of Health to attend their Annual General Meetings in the autumn of 1955.

Funds.—The past year had been characterized by an all-out effort to increase finances, and the generous contributions of many friends and supporters had made possible the significant developments reported. A special appeal to industry had been launched at a dinner at the Mansion House on October 13, by kind permission of the Lord Mayor (the Rt. Hon. Sir Noel Bowater, Bt.), and the occasion had been graced by the presence of the President, H.R.H. the Duke of Gloucester. A very generous response to this appeal had been received, and funds had also been raised by a B.B.C. Sunday evening appeal, and a film première at the London Casino, by courtesy of the Variety Club of Great Britain.

Report of the William Marsden Travelling Professor, 1953-54*

This tour started in August, 1953, and ended in September, 1954.

Starting with the Eighth International Congress of Rheumatic Diseases, held at Geneva in August, 1953, the tour went through Zürich and Berne, continued in Paris, the Netherlands, Copenhagen, Malmö, Stockholm, and Uppsala, and reached the U.S.A. in March, 1954.

Europe.—A most friendly and hospitable welcome was received in all of the countries mentioned. I was particularly struck by connective tissue research and by research into the mode of action of the adrenocortical and pituitary hormones. Rehabilitation is taking a more important place than was the case a few years ago. A point of special interest was the university work in Paris, Amsterdam, Copenhagen, and Sweden. It is difficult to pick out one particular aspect, but perhaps Teilum's work in Copenhagen on amyloidosis and Asboe-Hansen's work on mast cells were outstanding. During the European tour I gave two papers to the International Congress on viscosity of synovial fluid and

* A full report is available for members of the Heberden Society and Empire Rheumatism Council who would care to see it.

electrophoresis of serum proteins in rheumatoid arthritis. In addition I gave lectures to the University of Lund and to the Dutch and Swedish medical societies.

United States.—Here I visited centres in New York, Boston, Philadelphia, St. Louis, the Mayo Clinic, Chicago, Ann Arbor, Cleveland, Washington, San Francisco, and Vancouver, B.C., and gave eight lectures. Perhaps Ann Arbor was the most interesting centre, but I also saw much good work in New York and Chicago. In San Francisco I gave a talk to the American Rheumatism Association. Finally I visited the University of Vancouver.

A tour of this sort gives the opportunity of seeing many different points of view and many different ways of tackling the same problems. I am grateful to the Board of Governors and the Endowment Fund Sub-Committee of the Royal Free Hospital.

ERNEST FLETCHER.

CONSULTANTS COURSE ON MODERN ASPECTS OF RHEUMATIC DISEASE

This course, which was held on March 24 to 26, 1955, at the Middlesex Hospital and the Postgraduate Medical School of London, was attended by fifty consultants. The opening address by Sir Francis Fraser was followed by a series of papers and discussions:

Prof. J. H. Kellgren: Differential diagnosis of polyarthritis.
Prof. D. H. Collins: Pathology of rheumatoid arthritis.
Dr. E. G. L. Bywaters: Rheumatoid arthritis and its variants.
Dr. J. J. R. Duthie: Anaemia and rheumatoid arthritis.
Dr. O. Savage, Dr. J. J. R. Duthie, and Dr. H. F. West: Cortisone and ACTH in rheumatoid arthritis.
Dr. Ifor Williams: Recent advances in the radiology of rheumatoid arthritis.
Panel discussion on the management of the rheumatoid arthritic, conducted by Prof. Kellgren, Dr. Tegner, and Dr. Duthie.
Dr. F. Dudley Hart: Ankylosing spondylitis.
Dr. J. Sharp: Atypical ankylosing spondylitis.
Dr. R. M. Mason: Uric acid and acute gout.
Dr. F. G. W. Marson: Treatment of chronic gout.
Prof. J. H. Kellgren: Clinical syndromes of osteo-arthritis.
Mr. M. H. M. Harrison and Mr. G. C. Lloyd-Roberts: Discussion on osteo-arthritis.
Panel discussion conducted by Prof. Hartfall, Dr. Kersley, Dr. Harrison, Dr. West, Mr. Lloyd-Roberts, and Mr. W. D. Coltart.
Series of demonstrations and discussions on the Use and Interpretation of Serological Tests in the Rheumatic Diseases.
Clinico-pathological conference conducted by Dr. Fearnley, Dr. Gilliland, Dr. E. G. L. Bywaters, and Dr. M. H. M. Harrison.

HEBERDEN SOCIETY

At a Clinical Meeting held at the Royal Free Hospital, London, on February 18, 1955, the following papers were given:

DR. J. H. JACOBS (*Royal Free Hospital*): Studies on Hyaluronic Acid of Synovial Fluid.

By means of exact viscosity studies (Scott, Blair, and others, *Biochem. J.*, 1954, **56**, 504), a comparison was made between the degree of polymerization occurring in the synovial hyaluronic acid in cases of rheumatoid arthritis and non-generalized osteo-arthritis.

Two different aspects of molecular complexity were investigated as measured by anomalous viscosity and limiting viscosity. From the results of such measurements, it appeared that there were no essential differences between these two aspects of molecular structure in the synovial hyaluronic acid of rheumatoid arthritis and osteo-arthritis.

A significant difference was found in the specific viscosity of synovial fluids in the two conditions, but this could be accounted for by the higher concentration of hyaluronic acid found in osteo-arthritis, and it was unnecessary, therefore, to assume different degrees of polymerization to account for this difference in specific viscosities.

DR. F. CLIFFORD ROSE (*Royal Free Hospital*): Masked Pneumonia occurring during Cortisone Therapy.

This paper reported three deaths from pneumonia in patients under treatment with cortisone or ACTH. In all cases the mode of onset of the pneumonia was unusual and the relationship between the physical signs and the clinical duration of the disease atypical. The pathological findings in the adrenals could be correlated with the hormone therapy received. In one, who had received continuous cortisone for 6 weeks before death, there was evidence of atrophy and conspicuous degenerative changes and haemorrhage in all three zones of the cortex. In spite of the possible enhancing effect of cortisone on invasion by organism, the drug should not be stopped on the diagnosis of infection, as such patients when undergoing extra stress, may develop a relative hypo-adrenal state and therefore require a higher dosage of cortisone.

This need for extra adrenal hormones overrides the danger of the bacteraemia which can be controlled by antibiotics.

MR. R. L. MARKHAM (*Royal Free Hospital*): Paper Electrophoresis of Serum Mucoproteins.

Paper electrophoresis of serum carried out at *p*H 4·6, with the filter paper clamped between glass plates, was shown to produce a separation of two mucoprotein fractions—M-1 and M-2, and it was demonstrated that these travel with alpha$_1$ and alpha$_2$ globulins respectively at *p*H 8·6.

Experiments on isolated fractions eluted from the filter paper indicated that M-2 is removed by co-precipitation with albumin when sulphosalicylic acid or perchloric acid is added to serum, but M-1 remains in solution.

Mucoprotein levels were increased above the levels found in fifteen normal sera, in thirty sera from patients with active rheumatoid arthritis, and in five patients with ankylosing spondylitis. The levels of the two fractions appeared to be related and showed an overall correlation with the erythrocyte sedimentation rate. Changes in the alpha$_1$ and alpha$_2$ globulin fractions of the same sera observed on electrophoresis at *p*H 8·6 appeared to be due mainly to the raised mucoprotein levels.

*DRS. ALLAN ST. JOHN DIXON, SAVITRI RAMCHARAN, and MARION ROPES (*Canadian Red Cross Memorial Hospital, Taplow*): "Rheumatoid Arthritis: Dye Retention Studies and Simultaneous Comparison of Dye and ^{51}Cr-labelled Red Cell Methods for the Measurement of Blood Volume."

Two unusual cases were demonstrated, one of "Shoulder-hand Syndrome", by DR. A. T. RICHARDSON, and the other of "Lupus Disseminatus Erythematosus", by DR. E. HESS.

Demonstrations were set up to show the measurement of synovial fluid viscosity, the electrophoretic pattern of blood mucoproteins, and joint temperature measurement.

Heberden Round.—This was held at The Westminster Medical School, Horseferry Road, London, on May 6, 1955, and was conducted by Dr. F. Dudley Hart.

A report was presented of the Empire Rheumatism Council Cortisone-Aspirin Long-term Trial (Merck) by the following speakers:

DR. E. G. L. BYWATERS: Design and planning of the trial.

DR. IFOR WILLIAMS: Assessment of radiological change.

MR. E. LEWIS-FANING: Results up to one year, and statistical evaluation of clinical, laboratory, and radiological data.

Dr. F. Dudley Hart summed up, and the series of papers was followed by a discussion.

* *Annals of the Rheumatic Diseases* (1955), **14**, 51.

FIRST PAN-AMERICAN CONGRESS OF RHEUMATOLOGY, 1955

The Pan-American League for the Study and Control of Rheumatic Diseases, a branch of the International League against Rheumatism, has chosen the Brazilian Society of Rheumatology as organizer of the First Pan-American Congress of Rheumatology, which will be held at Rio de Janeiro and Saõ Paulo, from August 14-20, 1955. Three days will be occupied by scientific sessions and three by social entertainments for the delegates and their families.

The following subjects will be discussed:

(1) Rheumatoid arthritis (aetiology, pathogenesis, diagnosis, treatment, rehabilitation).
(2) Osteo-arthritis (aetiology, treatment).
(3) Extra-articular rheumatism (shoulder-hand syndrome, sciatic syndrome, painful shoulder).
(4) Rheumatic fever (aetiology, pathogenesis, treatment).
(5) Basic studies on the collagen diseases.
(6) Free themes.

A detailed programme will be available shortly. Besides Brazilian doctors, the foremost exponents of world rheumatology have been invited to lecture. Applications for registration and scientific papers should be sent in as soon as possible.

Dr. Waldemar Bianchi (*General Secretary*),
Av. Franklin Roosevelt, 126-S/504,
Rio de Janeiro, Brazil.

Dr. Décio Olinto (*President of the Congress*).

RHEUMATIC UNIT AT EDINBURGH

A Rheumatic Unit with thirty beds was started in 1947 in the Northern General Hospital, under the direction of Dr. J. J. R. Duthie, Senior Lecturer in Rheumatic Diseases in Edinburgh University. On April 30, 1955, an extension was opened by the Minister of State, consisting of two single-storey blocks, one devoted to clinical work and laboratories and the other to staff rooms, offices, a photographic suite, and six consulting rooms with adequate waiting space. The cost of this was £27,000, which has been provided by the Nuffield Foundation.

OBITUARY

DR. CHARLES WILLIAM BUCKLEY

Readers of the *Annals* will be sorry to learn of the death of Dr. C. W. Buckley, who was until 1953 the Editor. Buckley might perhaps be regarded as the first European rheumatologist in the modern sense of the term, as he was the pioneer of our present approach to the subject. Practising as he did in a Spa at a period when the empirical outlook was universal, he maintained that the study of the rheumatic diseases must be objective and be regarded as a branch of internal medicine. In this way, as the result of systematic and accurate observation over a long period, he advanced the subject, and brought it for the first time in this country to the serious notice of the leaders of academic medicine. This service was acknowledged in 1933 by his election to the Fellowship of the Royal College of Physicians, which was at that time an unusual distinction amongst provincial physicians.

It was only last year that a special number of the *Annals* was dedicated to Dr. Buckley on the occasion of his 80th birthday, and readers will remember the tributes there paid to him and his work. In these circumstances, therefore, we need now only reproduce the anonymous obituary notice which appeared in *The Times* on May 31.

Rheumatic Disease and Its Cure

Dr. Charles William Buckley, M.D., F.R.C.P., a distinguished authority on rheumatic diseases, died on May 28, 1955, in his eighty-first year.

Born on October 10, 1874, the son of the late Henry Buckley, of Derby, he was educated privately and at St. Mary's Hospital, London, where he was an entrance scholar and Kerslake scholar in Pathology and Bacteriology and qualified M.B., London, in 1898, becoming M.D. in 1899 and F.R.C.P. in 1933. He was senior physician to the Devonshire Hospital for Rheumatic Diseases, Buxton, consulting physician to the Buxton District Hospital, and lecturer in chronic arthritis and rheumatic diseases at the British Post-graduate Medical School of the University of London.

During the war of 1914-18 he was an honorary major of the Canadian A.M.C. He was later president of the Heberden Society and of the Section of Balneology and Climatology of the Royal Society of Medicine. Besides contributions to the *Proceedings of the Royal Society of Medicine* and the *British Encyclopaedia of Medical Practice*, the *Index of Treatment* and various medical journals on his specialty, he published a work in 1938 entitled *Arthritis, Fibrositis and Gout*.

Buckley did valuable work both in the national and in the international sphere in his specialty. He took a prominent part in the committee work which began in the Royal College of Physicians and led eventually to the Empire Rheumatism Council. He helped materially on the literary side also, editing proceedings and journals dealing with rheumatism. In a field where "quackery" is all too frequent and where even medical men produce "cures" with little scientific basis, Buckley kept a clear mind and a critical faculty which often steadied the over-enthusiastic junior without being too discouraging. He saw clearly what spas could do and what they could and should not attempt. In this again his part, although not always popular, was important and in keeping with his scientific outlook. Buckley's reward will be seen in the gradual conquest of the chronic rheumatic disorders which will surely come as industrial and social medicine becomes fully developed.

He married Lilian, daughter of the late Hugh Hughes, of Manchester, and had one son and three daughters.

Ann. rheum. Dis. (1955), **14**, 214.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Rheumatic Pneumonia. (Pneumonia Reumatica.) NUSSENZVEIG, I., NOGUEIRA CARDOSO, M. A., PIMENTA DE CAMPOS, E., TRANCHESI, B., NUSSENZVEIG, V., and SONNTAG, R. (1954). *Arch. Inst. Cardiol. Méx.*, **24**, 55. 15 figs, 48 refs.

In this paper from the University of São Paulo, Brazil, the authors review the extensive literature on rheumatic pneumonia, and point out that the difficulty has always been to decide whether rheumatic fever can give rise to a specific pneumonia, or whether the pulmonary changes are secondary to heart failure. (Most workers admit the specificity of the changes.) They then report the findings in ten fatal cases of rheumatic pneumonia confirmed at necropsy. In all cases there was active pancarditis. In most of them the onset of the pneumonia was sudden, and was characterized by rapid breathing, cyanosis, and restlessness, while sweating was frequently excessive. Physical signs in the lungs were always less than expected. The radiological signs were fleeting, areas of consolidation clearing up and then re-appearing elsewhere. Post mortem the lungs were found to be of a rubber-like consistency; histologically the main changes were fibrinoid necrosis of the alveolar walls, with erythrocyte and mononuclear exudation, and hyaline degeneration of the interstitial tissue. In only one case were Aschoff nodes found in the affected tissue.

The onset of pneumonia in rheumatic fever aggravates the prognosis, and death, usually about the ninth day, occurs from respiratory failure. These cases occurred before ACTH was introduced and the usual drugs then available were found to be without effect.

Paul B. Woolley.

A Study of the State of Vessel Permeability in Juvenile Rheumatism. (К вопросу о состоянии сосудистой проницаемости при ревматизме у детей) SOKOLOVA-PONOMAREVA, O. D., and BISYARINA, V. P. (1954). *Pediatriya*, No. 5, p. 3.

The authors consider that rheumatism is an infective–allergic illness in which at all stages functional and morphological changes occur in the blood capillaries. They report that in a study of ninety children suffering from acute rheumatic conditions, including 38 cases of joint disease, 32 of cardiac forms of rheumatism, and twenty of chorea, an annular rash was observed in one-third of the 46 children suffering from a first attack and in one-half of the 44 children having a second or subsequent attack. The capillary permeability was measured at least twice in each child by Landis's method (the number of leucocytes found in the tissue fluid expressed as a percentage of the total leucocyte count) and showed that:

(1) a regular increase of capillary permeability was present in the active phase of all the forms of rheumatism studied, migration of leucocytes into the tissues occurring in 91 per cent. of the ninety cases;

(2) in the joint and cardiac forms of rheumatism capillary permeability was increased by 5·3 to 6·5 per cent. in the first attack and still further increased (by 7·5 to 8·9 per cent.) in the second or subsequent attacks. In chorea, however, although capillary permeability was increased also in the first attack (7·53 per cent.) in second or subsequent attacks it was decreased (by 4·76 per cent.).

(3) Improvement in the clinical state after a first attack of all the forms of rheumatism discussed was accompanied by a decrease in the capillary permeability, but in recovery from a second or subsequent attacks (except of chorea) there was no further decrease in vessel permeability concurrently with clinical improvement.

E. D. Fox.

Vitamin A in Rheumatic Fever. JACOBS, A. L., LEITNER, Z. A., MOORE, T., and SHARMAN, I. M. (1954). *J. clin. Nutr.*, **2**, 155. 2 figs, 7 refs.

The blood carotenoid and vitamin A levels were studied in relation to body temperature and the erythrocyte sedimentation rate (E.S.R.) in 100 patients with acute rheumatism. For purposes of comparison similar observations were made in patients suffering from pneumonia, subacute rheumatism, pleural effusion, rheumatoid arthritis, erythema nodosum, and acute tonsillitis. A fall in the vitamin A level was observed in association

with a rise in temperature, and although there was general correlation, this inverse relationship did not always hold good in each individual case. Similarly, there was a general tendency for the vitamin A level to fall with a rise in the E.S.R., but the vitamin A level did not fall as rapidly in rheumatoid arthritis with changes in the E.S.R. as it did in other conditions. A considerable fall in the blood vitamin A level was observed in the 14 days preceding death, and also in the vitamin A content of the liver in cases of heart disease due to rheumatic fever.

The authors are careful not to infer that rheumatic fever is different from any other infective process or that the changes in the vitamin A level are in any way specific for rheumatic infections. They merely conclude that because the level is reduced in rheumatic fever daily administration of 40,000 to 50,000 international units of vitamin A is reasonable adjuvant therapy.

R. E. Tunbridge.

Cortisone and Salicylates in Rheumatic Fever. HOLT, K. S., ILLINGWORTH, R. S., LORBER, J., and RENDLE-SHORT, J. (1954). *Lancet*, **2**, 1144. 1 fig., 9 refs.

A preliminary report is presented from the University of Sheffield on a controlled trial of cortisone and salicylates in high dosage in the treatment of rheumatic fever which was carried out at the Children's Hospital, Sheffield, on thirty children ranging in age from 4 to 14 years. They were divided into three equal groups.

Group 1 were given sodium salicylate in sufficient dosage to give a serum salicylate level of 30 to 40 mg. per 100 ml., the maximum daily dosage given being 150 grains (10 g.) per day. In addition, this group received 200 mg. of cortisone by mouth daily at first, the dose being reduced in steps to 50 mg. a day in 5 weeks.

Group 2 were given sodium salicylate alone, the dosage being adjusted to give the above blood salicylate level.

Group 3 received a lower dosage of sodium salicylate (20 to 30 grains (1·3 to 2 g.) daily). In each group treatment was continued until the erythrocyte sedimentation rate (E.S.R.) was normal on three consecutive occasions at weekly intervals.

Only the effect on the E.S.R. is reported here; this rate fell significantly more rapidly when the drugs were used in combination than when salicylates were given alone either in high or low dosage, and the average duration of treatment and therefore the period in hospital was considerably shorter in Group 1 than in Groups 2 and 3.

[This is only a preliminary report on a small number of cases, but it comes from such an authoritative source that the findings must arouse considerable interest.]

Oswald Savage.

Salicylates in Rheumatic Fever. Difficulties experienced in treating Children with Large Doses. HOLT, K. S. (1954). *Lancet*, **2**, 1197. 3 figs, 19 refs.

Difficulties experienced in the treatment of rheumatic fever with large doses of salicylates are described. Between 1948 and 1954 a total of 52 children, aged 4 to 14 years, with rheumatic fever, received 58 courses of salicylate, the dosage employed being sufficient to achieve a serum salicylate level of 30 to 40 mg. per 100 ml. In twelve of the courses cortisone was given in addition. Frequent adjustments (totalling 172) had to be made in the dosage to maintain the desired blood level. Toxic symptoms were common. Hyperpnoea occurred thirty times in seventeen cases; on eighteen occasions it was the only toxic symptom; on five occasions it was associated with vertigo, on four with drowsiness, on two with nausea and vomiting, and on one occasion with deafness. Only two children complained of tinnitus, while three complained of deafness. It was notable that neither tinnitus nor deafness occurred on the eighteen occasions when hyperpnoea coincided with a high serum salicylate level. The author concludes that since the incidence of toxic symptoms was so high treatment with large doses of salicylates should always be carried out in hospital, where adequate supervision is possible. *R. S. Illingworth.*

Sequelae of Rheumatic Fever in Men. Four to Eight Year Follow-up Study. ENGLEMAN, E. P., HOLLISTER, L. E., and KOLB, F. O. (1954). *J. Amer. med. Ass.*, **155**, 1134. 16 refs.

The sequelae of rheumatic fever in adults were studied at the University of California with reference to the medical records and present condition of 135 ex-Service men who had rheumatic fever during the war, the records of a further eighty ex-Service men who had had rheumatic fever but who were not followed up being used for comparison. The patients, whose average age was 22 years, were examined clinically and radiologically and questioned about symptoms and physical fitness.

It was found that while many had symptoms of heart disease (precordial pain, dyspnoea, and palpitation) only 32 (23·7 per cent.) had definite rheumatic heart disease at the time of the follow-up examination, although 69 were considered to have rheumatic carditis during the initial attack. In none of the patients was there clinical or radiological evidence of arthritis, although 89 complained of pain and stiffness in joints. A few of the patients had to avoid arduous physical work and competitive sports, but 95 per cent. were either employed or attending college, the remaining 5 per cent. being unemployed because of non-rheumatic disease or psychiatric disorder.

Examination of the records of the eighty control subjects showed that sixteen had signs of rheumatic carditis about 3 years after the attack of rheumatic fever, although carditis was present in 35 at the time of the attack. The authors comment on and compare these results with those obtained in similar studies of rheumatic fever in juveniles. *Kathleen M. Lawther.*

Epidemiological Relationships between Scarlet Fever and Acute Rheumatism. (Über epidemiologische Beziehungen des Scharlachs zum akuten Rheumatismus.) HÄSSLER, E. (1954). *Z. Rheumaforsch.*, **13**, 215. 1 fig., 15 refs.

The association between scarlet fever and acute rheumatism formed the subject of a study carried out in the German town of Chemnitz between 1950 and 1953. During that period an increase in the incidence of scarlet

fever was accompanied by a parallel increase in that of acute rheumatism. Whereas ten cases of acute rheumatism were reported in each of the years 1946 and 1947 (when there was no scarlatina epidemic), the figure for 1950 was 117, and for 1851 it was 100. Although few of the patients developing rheumatic fever showed any signs of a prodromal scarlatiniform eruption, 22 children with scarlet fever (usually slight) showed evidence of cardiac damage without joint involvement, and in a few others chorea minor was noted. A plea is made for early and intensive penicillin therapy in all haemolytic streptococcal infections. *D. Preiskel.*

Abortive Rheumatic Fever. (Die abortive Polyarthritis rheumatica acuta.) LEU, H. J. (1954). *Praxis*, **43**, 913. 25 refs.

It is suggested by the author that rheumatic fever is frequently met with nowadays in an atypical and less florid form, and that more attention should be paid to abortive cases. The change in the nature of the disease is ascribed to mutations in the streptococcal population as a result of the widespread use of antibiotics.

Ten cases of the abortive form were noted in the course of one year (mainly in the spring) at the Swiss Military Hospital at Novaggio in apparently healthy recruits aged between 20 and 23. Single or multiple joints became painful and swollen, but the body temperature was not raised and the erythrocyte sedimentation rate (E.S.R.) was increased in only a few cases. Serum antistreptolysin titres were usually normal or slightly raised, and the agglutination reactions for haemolytic streptococci were negative in all cases. There was no anaemia, no leucocytosis, and no lymphocytosis or shift to the left. Clinically, there was no evidence of endocardial damage and there was no electrocardiographic evidence of myocarditis. *X*-ray films of affected joints were negative. Salicylates gave dramatic results. All ten patients had chronic tonsillitis, and tonsillectomy was performed on nine of them, with excellent results—residual joint pain rapidly disappeared, the E.S.R. (where raised) fell to normal, and any albuminuria present cleared quickly.

The author discusses the classification of the collagen diseases and the differential diagnosis of his ten cases. *D. Preiskel.*

Incidence and Frequency of Infections at Specific Ages in Infancy and Childhood. With Special Reference to Upper Respiratory Infections in potentially Rheumatic Susceptible Children. EPSTEIN, N. (1954). *Amer. J. Dis. Child.*, **87**, 600. 3 figs, 9 refs.

Difficulties in the Diagnosis of Acute Rheumatism in Medical Practice. (Les difficultés du diagnostic de la maladie de Bouillaud en pratique médicale.) PILORGÉ, D. (1954). *J. Med. Chir. prat.*, **125**, 843.

Laboratory Aids in the Diagnosis of Rheumatic Fever and in Evaluation of Disease Activity. WOOD, H. F., and MCCARTY, M. (1954). *Amer. J. Med.*, **17**, 768. 1 fig., 23 refs.

Newer Concepts in the Diagnosis and Treatment of Rheumatic Fever. ADAMS, F. H. (1954). *J. Amer. med. Ass.*, **156**, 1319. 2 figs.

Recent Advances in the Diagnosis of Rheumatic Heart Disease. LUISADA, A. A. (1954). *Amer. J. Med.*, **17**, 781. 5 figs, bibl.

Salicylates in Rheumatic Fever. WILLCOX, P. H. (1955). *Med. Press*, **233**, 56. 10 refs.

Treatment of Rheumatic Fever. MCEWEN, C. (1954). *Amer. J. Med.*, **17**, 794. Bibl.

Use of Antibiotics for the Prevention of Rheumatic Fever. STOLLERMAN, G. H. (1954). *Amer. J. Med.*, **17**, 757. 1 fig., bibl.

Acute Rheumatism treated with Phenylbutazone in 23 Cases. (Vingt-trois cas de maladie de Bouillaud traitées par la phénylbutazone.) ABLARD, G., LARCAN, A., HURIET, C., GILGENKRANTZ, J. M., and GIRERD, G. (1954). *Bull. Soc. méd. Hôp. Paris*, 70, 952.

Chronic Articular Rheumatism

(Rheumatoid Arthritis)

Silicosis and Polyarthritis. (Silikose und Polyarthritis.) PETRY, H. (1954). *Arch. Gewerbepath. Gewerbehyg.*, **13**, 221. 2 figs, 24 refs.

The author was impressed by the frequency with which advanced silicosis appeared to be associated with rheumatoid arthritis in miners attending the Miners' Hospital at Hamm, and set out to determine whether the association was valid. Of 350 patients who had been diagnosed between 1947 and 1953 as having rheumatoid arthritis, 160 had not been exposed to a silicosis hazard. Of the remaining 190, all of them coal-miners, radiographs of the chest showed normal appearances in 61 per cent. silicosis of Stages I and II in 14 per cent., and silicosis of Stages II-III and III [equivalent to pulmonary massive fibrosis (P.M.F.) in the British classification] in 25 per cent. (48 cases). The proportion of cases of P.M.F. was thus very much greater than that found in field surveys of working miners in Germany, which is less than 1 per cent. Among 116 arthritic patients with a history of over 15 years' exposure to dust, 43 (37 per cent.) had P.M.F., whereas in the general population of German miners with 20 years' exposure and more the proportion is only 6 per cent., while of 100 patients attending the Hamm clinic for conditions other than arthritis who had worked underground for more than 30 years, only eight had P.M.F. The author concludes that there must be a real association between massive fibrosis and rheumatoid arthritis. This confirms the observations of Caplan and others (*Brit. med. J.*, 1953, **2**, 1231; *Abstracts of World Medicine*, 1954, **15**, 535), in South Wales, although in only one of the German cases was there the characteristic type of radiological appearance described by Caplan (*Thorax*, 1953, **8**, 29).

Among the patients with rheumatoid arthritis a high erythrocyte sedimentation rate was more frequently found in those with advanced silicosis than in the remainder. In twenty cases it was possible to determine accurately the dates of the onset of arthritis and of the first appearance of massive fibrosis, the arthritis developing first in eight, simultaneously with P.M.F. in five, and subsequently in seven cases. In only five cases was the onset of the two conditions separated by more than 5 years. Although tuberculosis was suspected on radiological grounds in 41 of the 48 cases of P.M.F. with rheumatism, the sputum in every case was negative for tubercle bacilli, so that the author does not agree with Caplan's suggestion that the arthritis may be due to pulmonary tuberculosis. He discusses various mechanisms whereby P.M.F. might predispose to rheumatoid arthritis, but can suggest no acceptable explanation for the undoubted association between the two conditions.

C. M. Fletcher.

Silico-Arthritis. (Silikoarthritis.) BAADER, E. W. (1954). *Z. Rheumaforsch.*, **13**, 258. 9 refs.

In reviewing recent work on the association between advanced silicosis and rheumatoid arthritis, the author points out that this association was reported almost simultaneously by Caplan in England and Colinet in Belgium, and had been recognized by Petry in Germany before either of these publications had appeared, while in Brittany the syndrome has been known as the "St. Roch disease" for many years. In place of the various eponymous designations which have been, or may be, applied to this syndrome, the author proposes the term "silico-arthritis". Altogether 178 cases of the syndrome have now been recorded in the literature, but the particular "rheumatoid" type of radiological appearances described by Caplan are rare.

While one case in which tubercle bacilli were eventually found in the sputum is described in detail, active tuberculosis is seldom proved during life in these cases and the author considers that the arthritis is more likely to be a secondary manifestation of silicosis, although its exact aetiology remains to be determined.

C. M. Fletcher.

Use of Placental Serum in the Treatment of Rheumatoid Arthritis. TUFTS, M. (1954). *Wis. med. J.*, **53**, 615. 6 refs.

Caplan's Syndrome. (La sindrome di Caplan.) CHITI, E. (1955). *Reumatismo*, **7**, 19. 6 figs, bibl.

Disturbances of Muscle Metabolism in Rheumatoid Arthritis. (Quelques aspects des perturbations du métabolisme musculaire dans la polyarthrite chronique évolutive.) SCOPINARO, D., RIVANO, R., and SOLARI, S. (1954). *Rev. Rhum.*, **21**, 841.

Juvenile Rheumatoid Arthritis. RALEIGH, G. W., and KOBES, H. R. (1954). *Amer. Practit. (Philad.)*, **5**, 954. 2 figs.

Autosensitization and Rheumatoid Arthritis. (Autosensibilisation et polyarthrites chroniques.) TOUSSAINT, J., and GAUDIN, G. (1955). *Reumatismo*, **7**, 48. 6 refs.

Problems of the Management of Rheumatoid Arthritis. DAVISON, S. (1954). *J. Mt Sinai Hosp.*, **21**, 165. 15 refs.

Rarity of Concurrence of Psychosis and Rheumatoid Arthritis in Individual Patients. Report of a Case. TREVATHAN, R. D., and TATUM, J. C. (1954). *J. nerv. ment. Dis.*, **120**, 83. 4 refs.

(Osteo-Arthritis)

Development and Nature of Osteo-Arthritis of the Hip Joint. PRIDIE, K. H. (1955). *Rheumatism*, **11**, 2. 9 figs.

(Spondylitis)

Ankylosing Spondylitis of Delayed Onset in a Woman. (Spondylarthrite ankylosante féminine à début tardif.) RAVAULT, P., BERTHIER, L., and DUPRÉ, A. L. (1954). *Lyon méd.*, **192**, 533.

(Miscellaneous)

Peripheral Neuropathy in Periarteritis Nodosa. HEATHFIELD, K. W. G., and WILLIAMS, J. R. B. (1954). *Lancet*, **2**, 673. 4 figs, 7 refs.

The authors describe one case of mononeuritis multiplex and eight cases of symmetrical neuropathy due to periarteritis nodosa seen in a practice covering four general hospitals in London. They note that the former condition is characteristic of periarteritis nodosa, while the latter is clinically indistinguishable from the symmetrical neuropathy which occurs in diabetes, acute infective polyneuritis, bronchogenic carcinoma, alcoholism, vitamin-B deficiency, pulmonary tuberculosis, and chronic progressive polyneuritis.

All the patients with symmetrical neuropathy had similar symptoms. There was shooting and burning pain in the legs, worse at night. Later, distal paralysis occurred, the extensor muscles being more affected than the flexor group. Muscle wasting, tenderness in the calf, and loss of vibration and position sense followed. The ankle-jerks were commonly absent, but the knee-jerks were retained. The arms become involved in three cases. Distinguishing features in this type of case are listed as: raised erythrocyte sedimentation rate, raised serum globulin level (shown by electrophoresis to be chiefly gamma globulin), and normochromic anaemia with a leucocytosis and a tendency to eosinophilia; the urine commonly contains protein, blood cells, and casts, and the blood urea level is raised. Cutaneous or subcutaneous nodules were found to be inconstant. At necropsy there was macroscopic evidence of arterial disease affecting heart, liver, kidneys, and intestinal tract. The most difficult differential diagnosis is from broncho-

genic carcinoma, since, as the authors point out, a normal chest radiograph does not exclude such a diagnosis.

[This is a valuable paper which should be read in full, as the case notes are instructive.] *Geoffrey McComas.*

Management of Low Back Pain. MAY, F. (1954). *Med. J. Aust.*, **2**, 697. 18 refs.

It is first pointed out that low back pain is such a common complaint among patients seen in hospital departments of physical medicine that the management of these patients warrants consideration. To achieve the best results a full history, with details of the mode of onset of the pain and any subsequent changes, and a careful examination are essential. The spine and lower limbs should be examined to elicit hip movements, areas of tenderness, sensation, reflexes, and Lasègue's sign. Procaine should be injected into tender areas and the examination repeated. When a preliminary diagnosis has been made, further investigations should include *x*-ray examination of the spine, tests for focal sepsis, and estimation of the erythrocyte sedimentation rate, the blood uric acid content, and the haemoglobin level. In females the vagina should be examined to determine whether a lesion of the cervix is present; in males a prostatic smear should be examined microscopically.

Common causes of backache are scoliosis, postural defects causing pelvic tilt, spondylolisthesis, developmental abnormalities, fibrositis, acute infections and toxic conditions due to focal sepsis, cervical or prostatic lesions, disk protrusion and joint lesions, degenerative arthritis, senile osteoporosis, ankylosing spondylitis, fractures, secondary malignant deposits, and osteitis condensansilii.

In the author's view, psychogenic backache is not common. He discusses each lesion and the differential diagnosis, and outlines appropriate treatment, including rest, immobilization, passive or active physiotherapy, and manipulation as indicated. *J. B. Millard.*

Rheumatism in the Brewing Industry. (Rheumatismus im Brauereigewerbe.) WELLIČ, J. (1954). *Z. Rheumaforsch.*, **13**, 206. 5 figs, 8 refs.

Workers in the brewing industry are exposed to climatic conditions favouring the development of rheumatic diseases—frequent and violent changes of temperature, high humidity, and draughts. Of 732 such workers interviewed by the author, 142 complained of rheumatic symptoms; of these, 117 were above, and 25 below, the age of 32. The value of prophylaxis is stressed—provision of drying facilities for wet clothes, and access to fresh air and sunlight. The author strongly condemns the practice of providing free alcohol for employees as leading to flushing of the skin and thus increasing the liability to chills.

[No attempt was made to differentiate between the various types of rheumatic disorder complained of.] *D. Preiskel.*

Ocular Findings in Systemic Lupus Erythematosus. COWAN, T. W. (1954). *Trans. Pacif. Cst oto-ophthal. Soc.*, **35**, 57. 8 figs, 2 refs.

A brief discussion of the salient points in the diagnosis of lupus erythematosus is given together with a full description of two cases. An interesting feature in both cases is that marked sclerotic changes occurred in the blood vessels whilst the patients were under observation. *J. Berkwon.*

Orthopaedic Treatment of Chronic Arthritis. KUHNS, J. G. (1954). *Missouri Med.*, **51**, 1002.

Subcutaneous Cellulitis or Fibrositis. (La cellulite ou fibrosite sous-cutanée.) WALTHARD, K. M. (1955). *Reumatismo*, **7**, 1. 27 refs.

Chronic Rheumatism in Brucellosis. (Reumatismo cronico en brucelosos.) MARTORELLI, J. (1954). *Rev. argent. Reum.*, **19**, 137.

Disk Syndrome

Cervical Spondylosis. BRAIN, RUSSELL (1954). *Ann. intern. Med.*, **41**, 439. 2 refs.

In this discussion of cervical spondylosis, a condition which may lead to much disability, the author points out that the three main sites of cervical disk protrusion are dorsomedial, dorsolateral, and intraforaminal, and that this protrusion is of two aetiologically distinct types, namely, nuclear herniation and annular protrusion; the former constitutes a fairly acute problem, but may, in some cases, through degeneration or spondylosis, lead to the latter. The main factor is age, the attendant loss of elasticity and dehydration of the intervertebral disks causing additional wear and tear on the adjoining vertebrae and thus leading to osteophyte formation, the very mobility of the cervical spine contributing to this sequence of events. To this must be added the contributory effect of trauma in some 20 to 30 per cent. of cases.

The neurological effects of this osteochondrous change may be upon the nerve roots, the cord, or on both. To some extent direct pressure is responsible, but indirect vascular effects—especially compression of the anterior spinal artery—play a part, and the intrinsic arterial disease in elderly patients may also have some influence. The effects of these factors may be increased by trauma, particularly forcible neck extension, and so produce in the cord a picture of myelomalacia. The symptomatology in the radicular cases comprises those of a brachial neuritis with certain additional features; thus, acroparaesthesiae, and a picture resembling progressive muscular atrophy, may be produced. The clinical results of damage to the cord are very variable; they are usually insidious, but with occasional acute exacerbations due to trauma, the chief symptoms being weakness of the lower limbs, numbness and clumsiness of the hands, radicular pain in the upper limbs, or variable wasting in the hands. The reflex and sensory changes vary with the level, and the degree and duration of the compression. Dissociated anaesthesia may be encountered. In most cases the cerebrospinal fluid is normal, but occasionally its composition and dynamics may suggest an obstruction in the subarachnoid space. Radiography should

be carried out in the erect, flexed, and extended positions, with antero-posterior and oblique views to show the foramina. Myelography may be necessary. It is stressed that radiographic evidence of spondylosis does not constitute proof of the fact that the neurological symptoms are due to this cause.

The differential diagnosis is often difficult since the condition may simulate motor neurone disease, disseminated sclerosis, subacute combined degeneration of the cord, and tumour, both intra- and extra-medullary; syringo-myelia is rarely simulated. The course in cases of cord lesions is one of slow deterioration, finally becoming stationary and leaving the patient in most instances disabled but able to get about. As to treatment, immobilization of the neck for several months is advised, first in a plaster collar, then in a plastic one. The author has not been impressed with the value of head traction, and manipulation he considers to be dangerous. In general, surgery is most likely to be successful when the patient is relatively young, the history short, the disk protrusion single rather than multiple, and the cardiovascular system in good state. Decompression is favoured rather than an attempt to remove an arteriorly-placed osteophyte. On the whole, a conservative approach is considered best. *Fergus R. Ferguson.*

Pain in the Neck. Based on a Study of 100 Cases. HART, M. (1954). *Ann. phys. Med.*, **2**, 90.

In discussing the results of treatment of 100 cases of pain in the neck at the Middlesex Hospital, London, the author stresses the value of obtaining a complete history which should include details of the social, personal, and family background, as in these cases a knowledge of the patient's personality is important. In all cases a routine general medical examination was carried out and also a detailed examination of the head, neck, shoulders, and upper limbs. The range of neck movements, pain on movement, and the distribution of referred pain were recorded. A routine radiological examination was also performed.

Of the 100 cases studied, 29 had solely organic lesions, such as degenerative joint disease or a cervical disk lesion to account for the symptoms; in 22 cases there was in addition a functional disturbance, such as chronic anxiety, cancerphobia, or a menopausal symptom; the remaining 49 cases were considered to be suffering from a wholly functional condition. It was noted that in general a history of short duration was associated with an organic lesion and one of long duration with a psychopathological lesion. The radiological findings were not diagnostic, but pathological changes were seen in 90 per cent. of cases with solely organic lesions and in 63 per cent. cases with a purely functional lesion.

The author makes some general observations on treatment, suggesting short-wave diathermy for degenerative joint disease, and the administration of analgesics and conservative treatment for cervical disk lesions. In degenerative joint conditions active neck exercises should be avoided, as they tend to aggravate the symptoms and in these cases some limitation of movement may have to be accepted. Psychogenic pain should be treated by the prolonged-interview technique of psychotherapy at monthly intervals, but the results are on the whole poor. *J. B. Millard.*

Motorized Intermittent Traction for Treatment of Herniated Cervical Disk. SHENKIN, H. A. (1954). *J. Amer. med. Ass.*, **156**, 1067. 4 figs, 2 refs.

Gout

Isotopic Uric Acid in Gouty and Rheumatoid Arthritis Patients treated with Probenecid and Phenylbutazone. BISHOP, C., BEYER, A., and TALBOTT, J. H. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **86**, 760. 6 refs.

In investigations carried out at Buffalo General Hospital (University of Buffalo Medical School), New York, the size of the body's uric acid pool and its rate of turnover were studied in patients with gout or rheumatoid arthritis. After a control period probenecid was given in doses of 1·5 g. daily for a week, followed by phenylbutazone, 400 mg. a day, for a further week. With both drugs, two patients suffering from rheumatoid arthritis showed a reduction in the size of the uric acid pool and an increase in the rate of turnover, but no increase in the urinary output of uric acid, whereas in three patients with gout and another with rheumatoid arthritis, in all of whom the serum uric acid level was abnormally high, there was an increase in uric acid output and again some reduction in the uric acid pool. The effect of probenecid seemed to be greater than that of phenylbutazone. *G. Loewi.*

Cortisone in Gout. (La cortisona en la gota.) RUIZ MORENO, A. (1954). *Arch. argent. Reum.*, **17**, 113.

General Pathology

Serum Polysaccharide—Protein Ratio (PR) as a Measure of Rheumatoid Arthritis Activity. PAYNE, R. W., SHETLAR, M. R., BULLOCK, J. A., PATRICK, D. R., HELLBAUM, A. A., and ISHMAEL, W. K. (1954). *Ann. intern. Med.*, **41**, 775. 3 figs, 5 refs.

It is known that the serum polysaccharide content is increased and the serum protein levels altered in patients with active rheumatoid arthritis. The serum polysaccharide : protein ratio (P.R.), obtained by dividing the serum polysaccharide concentration by that of the serum protein and multiplying by 100, was calculated in 103 cases of rheumatoid arthritis studied at the University of Oklahoma and Bone and Joint Hospitals, Oklahoma City, and compared with the normal value, which averages 1·76. It was found that increased clinical activity of the disease was accompanied by a corresponding rise in the P.R., and improvement in the clinical state by a fall. There was no significant correlation between the P.R. and the erythrocyte sedimentation rate, but a negative correlation was noted with the serum albumin content, which decreased as the P.R. increased. The ratio is also increased by other inflammatory conditions, cancer, and severe trauma, but the authors suggest that

provided these conditions are kept in mind, it provides a useful objective measure of activity in rheumatoid arthritis. *F. Clifford Rose.*

Evaluation of Electrophoresis in Rheumatic Fever. KROOP, I. G., HEFFER, E. T., and SHACKMAN, N. H. (1954). *Amer. Heart J.*, **48**, 612. 19 refs.

Fractionation of the plasma proteins by salting-out techniques has not shown any consistent diagnostic pattern in rheumatic fever, although reversal of the albumin/globulin ratio may occur. The plasma fibrinogen content may be elevated, particularly during the acute phases of the disease, but electrophoretic studies have not established a characteristic diagnostic pattern. The present authors have employed free solution electrophoresis, together with estimation of the erythrocyte sedimentation rate, blood fibrinogen level, and the protein flocculation and C-reactive protein tests to determine the presence of rheumatic activity, a total of forty electrophoretic determinations on 36 patients being carried out.

Decrease of the albumin fraction with reversal of the albumin/globulin ratio was the most frequent finding. The γ globulin fraction was raised in most cases of active rheumatic fever, irrespective of whether there was a preceding respiratory infection. The β globulin fraction was increased in seven out of thirty patients with rheumatic fever, and in two cases was the only electrophoretic abnormality; α_1 and α_2 globulin levels were elevated early or late in the disease, and in some cases persisted despite cessation of rheumatic activity. Elevation of the α_2 globulin fraction was frequently associated with non-rheumatic inflammation.

The authors conclude that a normal electrophoretogram may be obtained in the presence of rheumatic activity and, since abnormalities are found when the condition is clinically inactive, electrophoresis is of little value in determining the presence of rheumatic activity, but is strongly suggestive of this activity if a high β globulin level is found. *F. Clifford Rose.*

C-Reactive Protein Determination as a Measure of Rheumatic Activity. SHACKMAN, N. H., HEFFER, E. T., and KROOP, I. G. (1954). *Amer. Heart J.*, **48**, 599. 4 figs, 18 refs.

It has been shown that if a dilute solution of the somatic polysaccharide isolated from the body of the pneumococcus is added to the serum of patients with pneumococcal pneumonia, a precipitate is formed. This reaction is also observed in rheumatic fever, subacute bacterial endocarditis, abscess of the lung, tuberculosis, congenital syphilis, and measles, but does not occur with normal serum. The reactive substance, C-reactive protein, migrates on electrophoresis with the α globulin, probably the α_1 fraction. C-reactive protein is nearly always found in the serum of patients with acute rheumatic fever, but is of no specific diagnostic value in differentiating this from other febrile states; it is, however, a sensitive index of rheumatic activity, disappearing with subsidence of this activity (usually before the fall in the erythrocyte sedimentation rate (E.S.R.)) and reappearing after the withdrawal of ACTH or cortisone therapy.

In the present study, which is reported from the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, New York, the authors carried out the C-reactive protein test in 23 cases of acute rheumatic fever. They found the protein present in nine out of ten active cases and it disappeared in six out of eight on the institution of cortisone and hydrocortisone therapy, the earliest disappearance of the protein being on the 8th day of treatment. In twelve out of the eighteen cases tested after hormone therapy the test was positive, but in eight of these subsequently became negative. The E.S.R. remained elevated 1 to 8 weeks after the protein had disappeared, but patients were allowed to get up provided the C-reactive test was negative. In two cases the test remained negative in spite of rheumatic activity as evidenced by a raised E.S.R., tachycardia, and electrocardiographic changes. C-reactive protein was present in two patients with chorea and carditis, and since the test is always negative in uncomplicated chorea, it is suggested that a positive test result in chorea is indicative of the presence of carditis.

The authors conclude that the C-reactive protein test is a better guide to activity than the E.S.R., which may show protracted elevation despite an inactive clinical state. *F. Clifford Rose.*

Hyaluronidase Therapy of Inflammatory and Degenerative Joint Diseases. RÖSSING, P., and LUTTERBECK, H. (1954). *Rheumatism*, **10**, 76. Bibl.

A critical evaluation of the relationship of the hyaluronidase–hyaluronic acid system to rheumatic disease of the joints led the authors to try local subcutaneous injection of hyaluronidase in the treatment of inflammatory and degenerative diseases of the joints, the rationale being the utilization of the absorption-promoting properties of hyaluronidase to remove the joint swelling. In a variety of cases of rheumatic joint disease five to ten units of a hyaluronidase preparation, "kinetin", was injected subcutaneously "every second to fourth day in the neighbourhood of the affected joints". The dosage was kept low because a higher one commonly produced inflammatory reactions. In 53 out of 83 cases there was definite subjective and objective improvement; in fourteen cases no objective effect was observed, although some of the patients asserted that they were improved. Only one patient was apparently worse after this method of treatment. Degenerative diseases responded in the most satisfactory manner, as also did the group of diseases designated "acute infective arthritis" and "toxic-allergic rheumatoid". Results in rheumatoid arthritis were variable and bore no relationship to the stage of activity of the disease. In rheumatic fever the results were less impressive. Later this treatment was combined with the depolymerizing effect of short-wave irradiation, with an improvement in the results. Intra-articular injection, which was tried on several occasions, proved painful and gave no better results than subcutaneous injection. Negligible skin reactions were observed at the site of injection on only fifteen out of 800 occasions.

The authors incline to the view that the disturbance in the anabolism or catabolism of hyaluronic acid is the

essential aetiological factor in inflammatory and degenerative diseases of the joints. Hyaluronic acid is present in increasing amounts in the joints of rheumatic subjects "although of a lower degree of polymerization". They do not support the view that increased activity of hyaluronidase is an essential component in the pathogenesis; furthermore, they find that the increase in antihyaluronidase or serum inhibitors [like a number of other serum enzyme inhibitors] is a manifestation common to all inflammations and is not specific for rheumatism.

Harry Coke.

Clinical Usefulness of Electrophoretic Investigations of the Serum in Rheumatism in Childhood. (Zur klinischen Brauchbarkeit serumelektrophoretischer Untersuchungen beim Rheumatismus des Kindesalters.) FREISLEDERER, W., and STOEBER, E. (1954). *Z. Kinderheilk.*, **75**, 532. 11 figs, 15 refs.

Children with and without Rheumatic Fever. III. Blood Serum Vitamins and Phosphatase Data. WILCOX, E. B., GALLOWAY, L. S., WOOD, P., and MANGELSON, F. L. (1954). *J. Amer. diet. Ass.*, **30**, 1231. 26 refs.

Serum Proteins in Rheumatic Carditis. (Il quadro sieroproteico nelle carditi reumatiche.) CASOLO, G., and MAGGI, C. A. (1954). *Osped. maggiore*, **42**, 457. 3 figs, bibl.

Clinical and Experimental Observations on the Waaler-Rose Reaction in Rheumatology. (Observations cliniques et expérimentales sur la réaction de Waaler-Rose en rhumatologie.) ROBECCHI, A., and DANEO, V. (1954). *Rev. Rhum.*, **21**, 829.

Enzymes in the Mechanism of Inflammation in the Rheumatic Disorders. PETERMAN, E. A. (1954). *J. Mich. med. Soc.*, **53**, 1321. 7 figs, 28 refs.

Creatinuria in Rheumatic Disease. (Sulla creatinuria in malattie reumatiche.) RIVANO, R., SOLARI, S., and CURZIO, A. (1955). *Reumatismo*, **7**, 41. 37 refs.

Agglutination Reaction with Sensitized Erythrocytes as applied to the Serological Diagnosis of Rheumatoid Arthritis. II. Investigation of the Agglutinating Agent. (Über die zur serologischen Diagnose der chronischen Polyarthritis angewandte Agglutinationsreaktion mit sensibilisierten Erythrocyten. II. Untersuchungen über das die Agglutination vermittelnde Prinzip.) DICKGIESSER, F., and HARTER, F. (1954). *Z. ges. exp. Med.*, **124**, 501. Bibl.

Observations on the Pathology of Sjögren's Syndrome. CARDELL, B. S., and GURLING, K. J. (1954). *J. Path. Bact.*, **68**, 137. 6 figs, 12 refs.

ACTH, Cortisone, and Other Steroids

Clinical Investigation of Alleged Antagonism of Corticoids. GOULDING, R., MACLEAN, K. S., and ROBSON, J. M. (1954). *Lancet*, **2**, 775. 1 fig., 6 refs.

The authors describe an experiment devised and carried out at Guy's Hospital, London, to test Selye's hypothesis that antagonism between the "mineralo-corticoids" (such as deoxycortone) and the glucocorticoids (such as cortisone) is concerned in the pathogenesis of rheumatoid arthritis. For this purpose eight patients with acute rheumatoid arthritis were admitted to the hospital, given a normal diet, and encouraged to be ambulant as far as possible, no treatment other than physiotherapy and the administration of steroids according to the following schedule being given. In the first week 1 ml. sterile saline alone was given intramuscularly. Thereafter 100 mg. cortisone was given intramuscularly each day, in addition to the saline, until a satisfactory remission was obtained, the dose being then reduced to the minimal maintenance level. At this point 20 mg. deoxycortone acetate was next given each day in place of the saline (and in addition to the cortisone) for at least 7 days. In the final period of observation the maintenance dose of cortisone was given alone.

By the end of the first stage, while receiving cortisone alone, all eight patients were in satisfactory, if incomplete remission. No significant change in their condition occurred when deoxycortone was added, as judged by regular examination of the joints and determination of the fluid balance, body weight, blood pressure, erythrocyte sedimentation rate, eosinophil count, and serum sodium and potassium levels; nor was there any significant change when the deoxycortone was withdrawn and the cortisone continued.

From this admittedly small clinical trial the authors conclude that there is no evidence that deoxycortone exerts any adverse effect upon the protective action of cortisone in patients with rheumatoid arthritis. The possibility that other corticoids might have shown antagonistic action is briefly discussed, but is not considered very likely. *Robert de Mowbray.*

Antagonistic Effect of ACTH and Cortisone on the Anticoagulant Activity of Ethyl Biscoumacetate. CHATTERJEA, J. B., and SALOMON, L. (1954). *Brit. med. J.*, **2**, 790. 2 figs, 11 refs.

In an investigation of the causes of a high incidence of thrombo-embolic complications during administration of ACTH (corticotrophin) or cortisone, two female patients, one suffering from acquired haemolytic anaemia and the other from acute thrombophlebitis, were studied at Tufts College Medical School, Boston. ACTH was given in a dose of 80 to 100 mg. subcutaneously every six hours until the full therapeutic effect had been obtained, 20 to 25 mg. being given daily thereafter as a maintenance dose. Cortisone, in a dose of 150 to 200 mg. was administered orally or intramuscularly, the maintenance dose usually being one-quarter of this amount. Ethyl biscoumacetate ("Tromexan") was given daily in amounts varying from 300 to 1,200 mg., the exact requirement being judged from the plasma prothrombin activity, which was determined by a slight modification of the method of Quick; the plasma prothrombin conversion factor (P.P.C.F., labile factor) and the plasma fibrinogen levels were also determined.

The patient with haemolytic anaemia had developed thrombophlebitis during the administration of 100 mg.

cortisone daily. The serum contained auto- and iso-erythrocyte antibodies and the Coombs test was positive. On the institution of anticoagulant therapy wide fluctuations of prothrombin activity were noted. When the cortisone was discontinued a satisfactory therapeutic level of plasma prothrombin activity was easily obtained. Resumption of cortisone therapy was followed by a rise in plasma prothrombin activity, and the dose of ethyl biscoumacetate had to be increased to maintain a therapeutic level. Whereas the P.P.C.F. level showed no significant change, the plasma fibrinogen level, which had been high before the start of cortisone therapy, fell to normal levels on clinical and haematological improvement. In the second patient, who had acute thrombophlebitis, ACTH was found to increase the amount of ethyl biscoumacetate required to obtain an effective plasma prothrombin level, the requirement of anticoagulant falling again on decreasing the dose of ACTH.

The mechanism of this phenomenon is not clear, but some possibilities are discussed. Meanwhile, the authors recommend that, unless absolutely indicated for their known specific effects, ACTH and cortisone should be withheld in the presence of thrombo-embolic complications. *Norval Taylor.*

Use of Corticotrophin Gel as a Test of Adrenal Cortical Function. NABARRO, J. D. N. (1954). *Lancet*, **2**, 1101. 7 figs, 12 refs.

In carrying out tests for the diagnosis of Addison's disease the response of the adrenal cortex to stimulation with adrenocorticotrophic hormone (ACTH) has been shown to be influenced by the method of administration of the hormone. The author, who points out that intravenous infusion of the preparations of ACTH at present available is not without danger, has employed a recently introduced long-acting corticotrophin gel which is injected intramuscularly; he found that the best effects were obtained with a dosage of 120 units given on successive days. The adrenal response was estimated by determining the number of circulating eosinophil leucocytes, the ratio of urinary sodium to potassium excretion, and the level of 17-ketosteroid excretion, the following changes being regarded as significant:

(1) a fall in the absolute eosinophil count from over 50 per c.mm. to 10 or fewer per c.mm.;
(2) a reduction of the urinary sodium : potassium excretion ratio to 50 per cent. or less, of the initial level; and
(3) an increase in urinary 17-ketosteroid excretion of 4 mg. or more per 24 hours.

In a study carried out at University College Hospital, London, on 33 patients whose adrenocortical function was presumed to be normal, all of them showed significant alterations in the absolute eosinophil count, or of the urinary sodium : potassium excretion ratio, or both, after the first or second injection of ACTH gel. The excretion of 17-ketosteroids was increased significantly in all but four cases after the second injection, and probably would have been increased in all after a third injection. On the other hand, four patients with Addison's disease and two who had undergone total adrenalectomy showed no response after three to six injections ACTH gel, while six patients with panhypopituitarism responded after intervals of from 1 to 6 days. Finally, three patients suffering from adrenocortical atrophy as a result of prolonged treatment with cortisone showed a normal response to the test.

It is concluded that the absence of any significant change in the three indices mentioned above after three consecutive daily injections of 120 units corticotrophin gel strongly supports a diagnosis of Addison's disease. A suggested procedure for carrying out the test is briefly outlined. *A. C. Crooke.*

Occurrence of Electrocortin in Human Urine. COPE, C. L., and GARCIA-LLAURADO, J. (1954). *Brit. med. J.*, **1**, 1290. 5 figs, 18 refs.

Working at the Postgraduate Medical School of London the authors have examined extracts of urine from six normal subjects, four patients with rheumatoid arthritis, and three with congestive heart failure, for the presence of electrocortin, using a slight modification of the method of Tait and others (1952), who first described this adrenocortical steroid (*Lancet*, 1952, **1**, 122; *Abstracts of World Medicine*, 1952, **12**, 147). The method, which involves the use of adrenalectomized rats, is described in detail.

It was shown that a substance with sodium-retaining activity was present in small amounts in the urine of normal subjects, in that of one of the three cardiac patients, but no trace of it was found in the urine of the rheumatoid arthritic patients. In all cases in which it was present the amount of sodium-retaining factor was very small and several attempts to increase the output of this principle were made, without success; for example, the urine of a normal subject maintained on a diet containing less than 0·5 g. sodium daily did not show any increase of the sodium-retaining factor, nor did that of a patient maintained on doses of corticotrophin which were large enough to provoke a marked increase in hydrocortisone output. By chance the authors discovered a patient suffering from severe potassium loss associated with chronic pyelonephritis who, although in sodium balance, was found to be excreting large amounts of the sodium-retaining substance in the urine. The results of chromatographic analysis of extracts of her urine made it highly probable that this substance was electrocortin; thus a high titre of electrocortin in the urine does not necessarily imply a condition of sodium retention. The relation of rate of urinary excretion to blood level of the hormone is tentatively discussed, but too little is known as yet to permit of any definite conclusions.

Robert de Mowbray.

Studies of 17-Hydroxycorticosteroids. IV. Evaluation of a Standard ACTH–17-Hydroxycorticosteroid Response Test in Children. ELY, R. S., RAILE, R. B., BRAY, P. F., and KELLEY, V. C. (1954). *Pediatrics*, **13**, 403. 1 fig., 30 refs.

Adrenal cortical activity is usually assessed from such factors as the eosinopenic response, urinary excretion of steroids, and water and electrolyte balance. It can be

determined more directly by the change in blood level of 17-hydroxycorticosteroids in response to intramuscular injection of ACTH. At the University of Utah College of Medicine, Salt Lake City, adrenocortical function was determined in this way in forty children suffering from various disorders and in forty healthy children aged 2½ to 16 years.

Before, and 2 hours after, intramuscular injection of 25 I.U. of ACTH, 30 ml. blood was withdrawn and the plasma level of 17-hydroxycorticosteroids determined by the method of Nelson and Samuels (*J. clin. Endocr.*, 1952, **12**, 519). The eosinophil count was also determined for each subject. In the control group the mean plasma concentration of 17-hydroxycorticosteroids was 12·0 μg. per 100 ml. before administration of ACTH and 29·8 μg. per 100 ml. afterwards. The difference was significant, but there was considerable variation between individuals, both in the initial level and in the degree of response (this variation was lessened somewhat if the response was assessed on the basis of body weight). Since a very low initial level was observed in several healthy children, the authors consider that this value alone is not an indication of inadequate adrenocortical function. In children with congenital hyperplasia, however, the initial plasma steroid level was consistently low (mean 2·6 μg. per 100 ml.), and there was no significant rise after administration of ACTH.

In fifty cases the observed rise in plasma 17-hydroxycorticosteroid level was compared with the degree of eosinopenia, but no correlation was found, suggesting that the eosinopenia induced by ACTH is not dependent upon an increase in circulating steroids.

In the authors' view this method of determining adrenocortical function has considerable value, but the results of a single test should not be interpreted too rigidly, since both a low initial plasma level of steroids and a poor response to ACTH are observed occasionally in healthy subjects. It is suggested that dosage based on body weight and giving the ACTH intravenously might improve the test by minimizing certain individual variations. *Nancy Gough.*

Effect of Cortisone on Calcium Metabolism in Sarcoidosis with Hypercalcaemia: Possible Antagonistic Actions of Cortisone and Vitamin D. ANDERSON, J., DENT, C. E., HARPER, C., and PHILPOT, G. R. (1954). *Lancet*, 2, 720. 6 figs, 29 refs.

The authors, from University College Hospital, London, describe four cases of sarcoidosis with the rare complication of hypercalcaemia accompanied by impaired renal function, and report the results of treatment with cortisone in doses ranging from 50 to 150 mg. daily. Calcium balance studies before treatment showed that faecal calcium was less than normal, the amount of calcium excreted being 33 to 75 per cent. of the intake instead of 85 to 90 per cent. After administration of cortisone the faecal excretion of calcium increased and the plasma calcium level fell, thus reversing the metabolic effect of calciferol.

The authors believe that the hypercalcaemia in these cases may have been due mainly to over-absorption of calcium from the intestine as the result of abnormal sensitivity to calciferol, although erosion of bone by sarcoid deposits may have been a contributory factor. They suggest that cortisone and calciferol may have antagonistic actions. Since cortisone did not depress the serum calcium level in a case of hyperparathyroidism, the authors consider that the drug should be used to distinguish this form of hypercalcaemia from that found in sarcoidosis. *D. G. Adamson.*

Use of Glycyrrhizin after Bilateral Adrenalectomy. HUDSON, P. B., MITTELMAN, A., and PODBEREZEC, M. (1954). *New Engl. J. Med.*, **251**, 641. 6 figs, 6 refs.

An evaluation of glycyrrhizinic acid for the maintenance therapy of patients subjected to bilateral adrenalectomy is reported from the Francis Delafield Hospital, New York. Three patients who had undergone bilateral adrenalectomy for metastatic cancer of various kinds were given a daily dose of 4 g. ammoniated glycyrrhizin (*U.S.P.*), 1 to 3 months after the required minimum dose of cortisone had been established, cortisone being then progressively withdrawn. It was found that the patients could not be maintained indefinitely on glycyrrhizin alone (one patient died from adrenal insufficiency), but they could be maintained for periods of several weeks on glycyrrhizin and a small dose (5 mg.) cortisone. [The evidence that glycyrrhizin has a cortisone-like action seems suggestive only.] *G. A. Smart.*

Splenectomy, Cortisone, and Corticotrophin (ACTH) in the Treatment of Certain Blood Dyscrasias. ELLIOTT, R. H. E., and HYMAN, G. A. (1954). *Surgery*, **36**, 610. 44 refs.

The therapeutic value of splenectomy in certain blood dyscrasias is well established; treatment with adrenocortical hormones has been less uniformly successful. A review of the literature since 1950 shows that there have been few studies reported of the combined effects of splenectomy, cortisone, and corticotrophin (ACTH) in the treatment of these diseases. The present paper from the Presbyterian Hospital (Columbia University), New York, gives the results in 25 cases of such combined treatment and compares them with those in 21 similar cases treated by splenectomy alone without hormone therapy. The two groups included fourteen and eight cases respectively of thrombocytopenic purpura, six cases in each group of acquired haemolytic anaemia, and twelve miscellaneous cases of hypersplenism.

In none of the 25 cases treated with hormones pre- or post-operatively was there any instance of adrenal failure during or after operation, and there was no interference with wound healing. Of the fourteen patients with thrombocytopenic purpura, cortisone or ACTH produced satisfactory remissions in five cases and symptomatic improvement in five, while of the six cases of acquired haemolytic anaemia, beneficial results were obtained in three, but no improvement in the other three. In only one of the five cases of hypersplenism in this groupwas there any response to hormone therapy. The authors conclude from these results that in selected cases of thrombocytopenic purpura and acquired haemolytic

anaemia cortisone and ACTH may be used with advantage as a means of preparing patients for splenectomy, and post-operatively in tiding them over a difficult period.
John F. Wilkinson.

Three Cases of Collagen Disease treated with Corticoids. RICHARDS, D. G. (1954). *Brit. med. J.*, **2**, 777. 8 refs.

The author describes three cases of diffuse collagen disease seen at the Queen Elizabeth Hospital, Birmingham, two of which were ultimately thought to be cases of acute disseminated lupus erythematosus and one to be a case of systemic scleroderma. He emphasizes the difficulty of diagnosis when the onset of the illness is extremely acute and the general constitutional disturbance is so severe that it masks the focal manifestations which are a guide to diagnosis in less acute cases. In all three cases the response to administration of corticoids was marked. The author believes that the hormones were probably life-saving, and suggests that the response to cortisone is of some diagnostic significance in these cases.
Nigel Compston.

Other General Subjects

Effect of Fluoride in Drinking Water on the Osseous Development of the Hand and Wrist in Children. MCCAULEY, H. B., and MCCLURE, F. J. (1954). *Publ. Hlth Rep.* (*Wash.*), **69**, 671. 5 figs, 39 refs.

Exposure to fluoride in drinking water was studied for evidence of detrimental effects on skeletal calcification and bone development in children. Three groups of children aged 7 to 14 years, living in Lubbock and Amarillo, Texas, and Cumberland, Maryland, were selected on the basis of continuous exposure to their communal drinking waters, which contained fluoride in the amounts of 3·5 to 4·5 p.p.m. F, 3·3 to 6·2 p.p.m. F, and 0·1 p.p.m. F respectively. Radiographs were taken of the right hand and wrist of 2,050 children. From these *x* rays, the skeletal age was assessed and a quantitative index of ossification was determined.

No evidence, available by radiographs, was obtained which would indicate that there was any adverse effect on the carpal bones or on their growth and development as a consequence of the continuous use of drinking water containing approximately 3·5 to 6·2 p.p.m. F. These results confirm the safety of maintaining the fluoride level of public water supplies at about 1·00 p.p.m. F, by controlled fluoridation, for the reduction of tooth decay.—[*Authors' summary.*]

Ocular Changes in Osteitis Deformans (Paget's Disease) in relation to Arteriosclerosis. (Zur Frage der Augenveränderungen bei der Ostitis deformans Paget in Beziehung zur Arteriosklerose.) PIETRUSCHKA, G. (1954). *Klin. Mbl. Augenheilk.*, **125**, 171. 2 figs, 2 tables, 76 refs.

A case of Paget's disease with bilateral muscular degeneration is described, and the relation, if any, between macular degeneration and retinal vascular changes such as angoid streaks and Paget's disease, reviewed in the light of the literature.

Subsequently 21 cases of Paget's disease with skull involvement were compared to 35 cases without such involvement, but significant ocular changes were seen in each group, and conversely skull *x* rays in a number of instances of macular or retinal vascular diseases revealed no evidence of Paget's disease. Thus no obvious relationship appears to link the two disorders.
L. Cudkowicz.

Significance of the Reactivity of the Organism in the Development and Treatment of Rheumatic Joint Disorders. (Die Bedeutung der Reaktionslage des Organismus für die Entwicklung und die Therapie der rheumatischen Gelenkserkrankungen.) SCHOLZ, H., and STEFFEN, C. (1954). *Klin. Wschr.*, **9**, 479. 40 refs.

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